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PROCEEDINGS

Teachers' Seminar

on

Pharmaceutical Chemistry

1958

Footnote References

Held Under the Auspices of the

AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

and Supported by the

AMERICAN FOUNDATION FOR PHARMACEUTICAL EDUCATION

UNIVERSITY OF MINNESOTA — MINNEAPOLIS, MINNESOTA

Proceedings of the

Teachers' Seminar on Pharmaceutical Chemistry

July 13-18, 1958

HELD UNDER THE AUSPICES OF THE AMERICAN
ASSOCIATION OF COLLEGES OF PHARMACY

AT

College of Pharmacy

University of Minnesota

Minneapolis

Edited by
GEORGE P. HAGER
and
FRANK E. DiGANGI

The Teachers' Seminars Are Made Possible by the Support of
The American Foundation for Pharmaceutical Education

FORWARD

The University of Minnesota College of Pharmacy was the grateful host to the 1958 A.A.C.P. Teachers' Seminar on Pharmaceutical Chemistry. The privilege of serving the A.A.C.P. on this occasion was especially appreciated since the Seminar was a very appropriate contribution of the College to the celebration of Minnesota's hundredth anniversary of statehood.

The cordial attitude of the faculty was most aptly expressed by Vice President William T. Middlebrook in his address welcoming the faculty and registrants of the Seminar to the University of Minnesota campus. On the same occasion, at a buffet supper at Centennial Hall on Sunday, July 13, Dr. W. Paul Briggs, Secretary and Executive Director of the sponsoring agency, The American Foundation for Pharmaceutical Education, conveyed to the registrants the Foundation's greetings and the assurance of the Foundation's high esteem for the Teacher's Seminars. Dr. Louis C. Zopf, President of the American Association of Colleges of Pharmacy, under whose auspices the Teachers' Seminars are organized, keynoted the week-long deliberations with a discussion of objectives.

The committee that arranged the program of the Seminar, Frank E. DiGangi, Paul Jannke, George L. Webster, Allen I. White, and George P. Hager, Chairman, were keenly aware of the Seminar's objectives in solicitation of speakers and assignment of topics. Three mornings were devoted to the question, <u>What</u> should undergraduates be taught? Three afternoons were occupied with the problem, <u>How</u> should undergraduates be taught? <u>Who</u> should teach pharmaceutical chemistry? Discussions of training, objectives, evaluation, opportunities, and responsibilities removed any uncertainty regarding the identity of a properly qualified teacher of pharmaceutical chemistry. Lectures given during the closing hours of the Seminar were clear demonstrations of pharmaceutical chemistry's research productivity, and provided convincing answers to the all-important query, "<u>Why</u> should pharmaceutical chemistry be taught?"

Workshops which served also as tours of laboratories in the vicinity were provided through the splendid cooperation of the Veterans Administration Hospital (Drs. Leslie Zieve and Dr. Herbert Nagasawa), General Mills Central Research Laboratories (Dr. Norval G. Barker, Dr. Lowell Peterson, and Mr. James Nelson), Minnesota Mining and Manufacturing Company Pilot Plant (Mr. Alva Frye) and the College of Pharmacy (Mr. Robert E. Willette).

The Seminar faculty consisted of twenty-seven members. The program was attended by one hundred and thirty-one registrants, many of whom made excellent contributions to the discussions. In some cases, the registrant participating in a discussion, failed to identify himself. Hence his contribution, as recorded on tape and transcribed in the following pages must, unfortunately, remain anonymous.

Undoubtedly the registrants are aware of the many benefits deriving from the willing efforts of local individuals and groups too numerous to acknowledge more fully at this time. The committee is fully cognizant of its debt to the faculty, students,

and staff of the College of Pharmacy, to the ladies of the Local Chapter of Kappa Epsilon, to many of the University's services, including the Housing Bureau, the Audio-Visual Education Service, the Department of Protection and Safety, the Athletic Department, the Coffman Memorial Union Food Service, and others.

To the members of the Seminar Faculty, the Committee expresses sincere appreciation for the excellent program that can be attributed only to their fine talents and their willingness to share freely their wisdom and experience with the Seminar's registrants.

Particular gratitude must also be expressed to the American Foundation for Pharmaceutical Education whose generous financial support made the Seminar possible.

George P. Hager
Chairman

A. A. C. P. COMMITTEE

Frank E. DiGangi, Professor of Pharmaceutical Chemistry,
University of Minnesota, College of Pharmacy.

Paul Jannke, Professor Pharmaceutical Chemistry,
University of Connecticut, College of Pharmacy.

George L. Webster, Dean,
University of Illinois, College of Pharmacy.

Allen I. White, Professor of Pharmaceutical Chemistry,
State College of Washington, School of Pharmacy.

George P. Hager, Dean,
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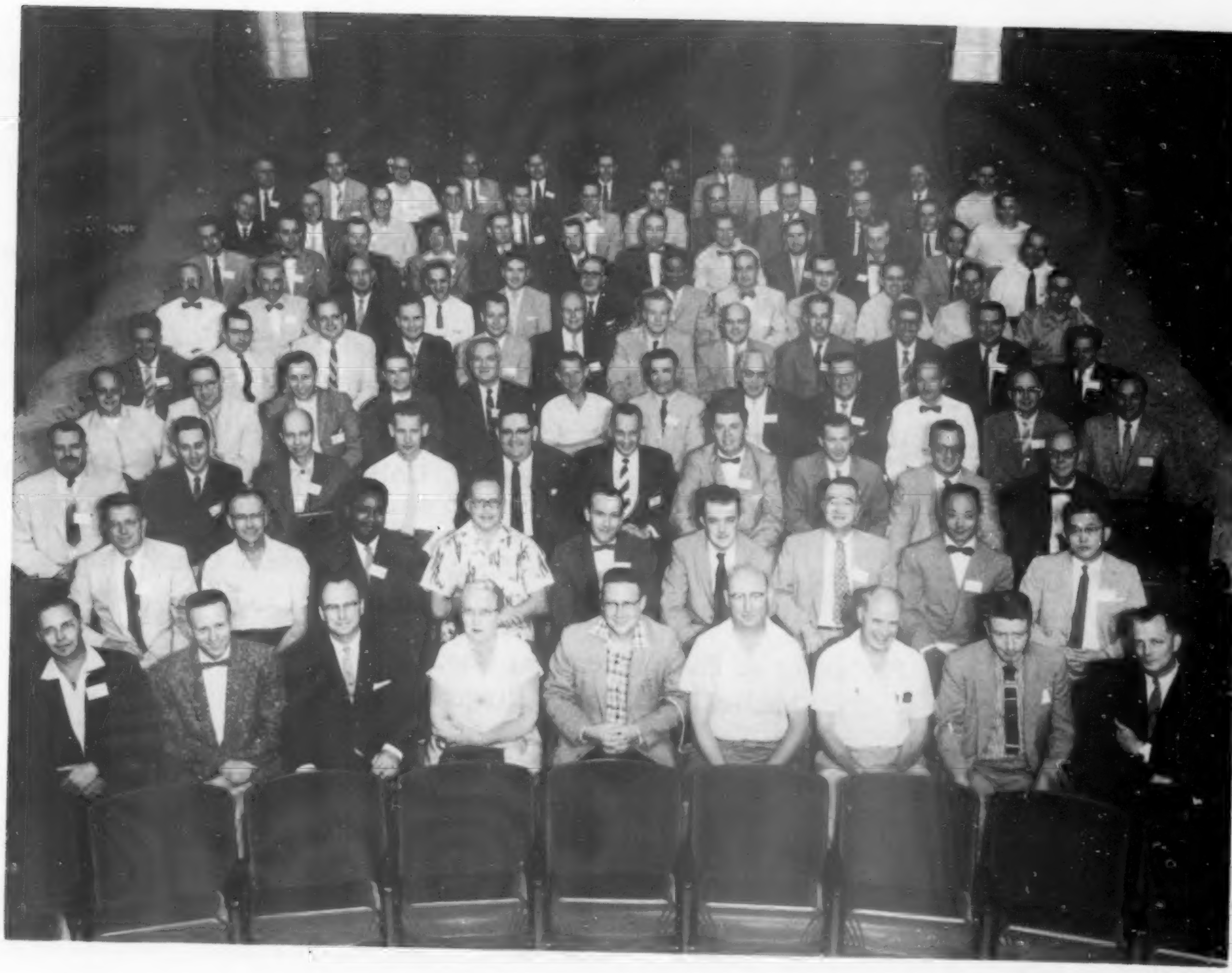

Teachers' Seminar, 1958

FACULTY

TEACHERS' SEMINAR ON PHARMACEUTICAL CHEMISTRY

Arnold H. Beckett -- Senior Lecturer and Director of Research, School of Pharmacy, Chelsea College of Science and Technology (London).

W. Paul Briggs -- Secretary and Executive Director, American Foundation for Pharmaceutical Education.

Bernard B. Brodie -- Chief, Laboratory of Chemical Pharmacology, National Heart Institute.

J. William Buchta -- Associate Dean, College of Science, Literature, and the Arts, University of Minnesota.

Joseph H. Burckhalter -- Professor of Pharmaceutical Chemistry, School of Pharmacy, University of Kansas.

Clarence A. Discher -- Professor of Pharmaceutical Chemistry, College of Pharmacy, Rutgers - The State University.

Ole Gisvold -- Professor of Pharmaceutical Chemistry, College of Pharmacy, University of Minnesota.

Melvin W. Green -- Director of Educational Relations, The American Council on Pharmaceutical Education.

Walter H. Hartung -- Professor of Pharmaceutical Chemistry, School of Pharmacy, Medical College of Virginia.

Harry W. Hind -- President, Barnes - Hind Laboratories, Inc.

Cyril J. Hoyt -- Associate Professor of Education, College of Education, University of Minnesota.

Ernst R. Kirch -- Professor of Chemistry, College of Pharmacy, University of Illinois.

Kwan-Hua Lee -- Associate Professor of Chemistry, School of Pharmacy, University of California Medical Center.

Arthur J. McBay -- Assistant in Legal Medicine, Medical School, Harvard University.

Alfred N. Martin -- Associate Professor, School of Pharmacy, Purdue University.

Robert H. Miller -- Associate Professor of Pharmacy, College of Pharmacy, University of Minnesota.

Maurice L. Moore -- Vice President, Vick Chemical Company.

Gordon M. A. Mork -- Associate Professor of Education, College of Education, University of Minnesota

Horace T. Morse -- Dean and Professor, General College, University of Minnesota.

W. Lewis Nobles -- Professor of Pharmacy and Pharmaceutical Chemistry, School of Pharmacy, University of Mississippi.

Milton O. Pella -- Professor of Education, School of Education, University of Wisconsin.

Justin L. Powers -- Editor, Scientific Edition, Journal of the American Pharmaceutical Association.

Edward E. Smissman -- Associate Professor of Pharmaceutical Chemistry, School of Pharmacy, University of Wisconsin.

Taito O. Soine -- Professor of Pharmaceutical Chemistry, College of Pharmacy, University of Minnesota.

George L. Webster -- Secretary-Treasurer, American Association of Colleges of Pharmacy.

Lee F. Worrell -- Associate Professor of Pharmaceutical Chemistry, College of Pharmacy, University of Michigan.

Louis C. Zopf -- President, American Association of Colleges of Pharmacy.

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Sunday Session

George P. Hager

Chairman

OBJECTIVES OF TEACHERS' SEMINARS

Louis C. Zopf
President, A. A. C. P.

Mr. Chairman, members of the Seminar, Ladies and Gentlemen. We are privileged to be in attendance at the 10th annual Seminar for Pharmacy Teachers co-sponsored by the American Association of Colleges of Pharmacy and the American Foundation for Pharmaceutical Education. The Pharmaceutical Survey of 1946 - 1949, under the directorship and guidancy of Dr. Edward C. Elliott and the committee appointed by the American Council on Education, recommended among other proposals that summer seminars for teachers of pharmaceutical subjects be put in operation beginning with the summer of 1949. The recommendation further stated, "the primary purpose of these seminars is that of providing needed opportunity for the members of the teaching staffs and for graduate students to come into fruitful contact and to keep pace with progressive content and methods of pharmaceutical teaching."

The first of these seminars was held in 1949 at the University of Wisconsin and was on the subject of pharmacy teaching. The educational philosophy of the teachers' seminars has been demonstrated to be sound as exemplified by the improvement in the curriculum patterns of our colleges of pharmacy and in the revision of much of the subject matter comprising the individual syllabi. The idea of seminars was not entirely new. Group discussions were and continue to be held under various names--such as short courses, conferences, workshops, etc. The idea was not exactly new to pharmacy, either. Through our Sections of Teachers of the American Association of Colleges of Pharmacy, we have had an opportunity, brief as it is, to review subject matter which is of specialized interest to the various divisions of pharmaceutical education. Unlike the Teachers Sections held at the time of our annual meeting, these seminars, with the exception of the general seminar, currently held every six years, are designed primarily for those persons teaching in a specialized division of pharmaceutical education. For example, as teachers of pharmaceutical chemistry, you are this week sharing experiences, ideas, and we trust discussing innovations for improved methods of teaching pharmaceutical chemistry in the colleges of pharmacy.

The initial objective of the Pharmacy Teachers' Seminar has very definitely been accomplished; namely, to improve the quality of teaching in our colleges of pharmacy. Until financial support became available from the American Foundation for Pharmaceutical Education, it was impossible for the American Association of Colleges of Pharmacy to offer their teachers opportunity to meet, for the exclusive purpose of considering the why and how of presenting pharmaceutical subject matter. Previous to this, the Sections of Teachers presented the only opportunity for specialty groups to meet and discuss problems of mutual interest. It is well known that the limited contact of the national meeting with its many diversions, affords little opportunity to bring forth any considered recommendations for improved teaching practices.

Our Teachers' Seminars permit us, to the extent desired, to exclude from discussion, and momentarily from our thinking, the other facets of pharmaceutical education; and thereby encourage a familial and uninhibited type of criticism with regard to course content, fundamentals and teaching methods, as well as evaluating the quality of teaching in the entire area of pharmaceutical chemistry. Some of us were fearful that these seminars would become a mutual admiration fraternity. Reference, however, to the pages of the proceedings of past seminars immediately dispels this fear. Here we find, quite to the contrary, that diverse opinions and multiple methods are presented on the same day and about the same subject matter. Conflicting ideas should encourage the experienced teacher--the so-called master--to review his syllabus and his teaching methods. It should also serve as a modifier or caution signal to the uninhibited, but sincere and energetic young teacher. Democracy shall continue to prevail at these seminars and seniority priorities have never been invoked.

The uninhibited discussion, exploration, and criticism of a teacher's methods by a fellow colleague strikes an indelible impression which is not only revealing to the recipient, but should elucidate methods of teaching for all who are under the same professional responsibility.

Dean Emeritus James B. Edmondson of the School of Education, University of Michigan, told the counterpart of this group six years ago during the meeting at Ann Arbor that, "most college teachers doubtless consider themselves to be effective teachers and some would rate themselves especially good. Such flattering self-evaluations are not surprising since few college teachers have ever had their instruction appraised by students or colleagues and few have ever been required to submit any evidence of their effectiveness in the classroom."

Review of the proceedings of the past seminars will confirm their compliance with the initial objectives of these special summer sessions. If doubting administrators need further evidence of the value of these seminars, then I refer them to the American Council on Pharmaceutical Education. The Council has evidence of improvement in teaching methods and curriculum design in the majority of the colleges of pharmacy during the past nine years. However, the efforts of the seminar committees have not gone unchallenged, and for the few doubters, I recommend they share in one of these conclaves and that they withhold further debasement until they have been participants and recipients of such an association for one week.

Having participated, one way or another, in each of our seminars has made me appreciate the foresight of the men who conceived the idea and saw the importance of such meetings. These men must be given credit for fearlessness and wisdom, as well as unusual courage to have the temerity to jar complacent teachers into the realization that they must continue to improve their methods of presentation, delete the old and present the new and startling materials in a manner which will be challenging to their students. At these seminars we have the opportunity to review methods and ideas and to correlate our activities with those of our fellow colleagues. Unlimited discussions at these conferences and the so-called after-conference "bull sessions" are a great help to all of us. Informality and fellowship have been the

keynote of the past seminar meetings and I hope will continue through all of our meetings. We encourage the young teacher to be expressive, but must we also remind you to respect norms and standards, particularly teaching standards. To challenge the present methods of teaching is noble, provided that you can be equally as fearless in your recommendations for constructive changes.

Dr. Lloyd E. Blauch, Chief for Education in the Health Professions, Department of Health, Education, and Welfare contributed much to the success of the Pharmaceutical Survey. I suggest we review the objectives which he outlined in 1954 for the Teachers' Seminar on Pharmaceutical Education at the University of Connecticut:

"The first objective of the seminar is to have the members review and comprehend some of the principles of learning with particular reference to the education of students of pharmacy....The second objective is for us individually to increase our knowledge about how to teach....The third objective will be to increase your desire to do your best teaching job....The fourth thing we hope to accomplish through this seminar is to increase materially the worthwhile literature on pharmaceutical education, particularly that which deals with the instructional and learning side....The fifth thing we expect to accomplish through this seminar is to improve our general education....The sixth objective is to become better acquainted with one another."

Although these objectives were designed primarily for the Seminar on Pharmaceutical Education, they are so fundamental that they defy better definition.

A decade will have passed with the conclusion of this Seminar and with its passing come new challenges and an increased responsibility for those of us who are in the field of higher education. The world has become concerned with educational patterns and it is currently a popular pasttime to be critical of the format of American education. Through these seminars, pharmacy is in about as good a position to answer the questions directed toward its educational program as are any of the areas of educational specialization. Pharmacy has had a rather recent critical evaluation of its curriculum. The survey revealed the weaknesses as well as the strong points of the profession--its practices, and its educational program. We have a more recent analysis of our position than any of the other professional groups unless it be Dentistry which is currently in the process of a critical survey.

During the six year interim since the first Seminar on Pharmaceutical Chemistry, you have been contributors to the development of a vast volume of literature and information regarding new chemical applications to pharmaceutical progress. We have acquired a list of new organic pharmaceutical medicinals during this decade of such proportion that their design, their therapeutic usefulness and their need must challenge even you, who serve as specialists in this area. The acknowledgement of this tremendous growth means that you have been forced to reorganize your entire subject matter so as to make it available to students in an informative, intriguing, and precise manner. Indoctrinating and encouraging students to be selective of worthwhile materials is an important attribute of the superior teacher.

A good teacher challenges his student's imagination. He outlines the objectives, with perhaps his greatest responsibility being that of organization of the course material so that the student achieves the defined objectives. Faculties of the colleges of pharmacy are frequently condemned because we teach what is lucidly referred to as too much scientific information and not enough know-how. Perhaps we should restate the age-old responsibility of the university--to convince students that learning is a life-long process and what they learn in school should not be the terminus of their educational experiences. It is a well-recognized fact that pharmacists are notoriously poor readers and I am confident that a part of this responsibility belongs in the hands of those of us who have been in the teaching program. Education and advancement of all professional and scientific fields continues as a revolution. Teaching must not become static; we cannot rely on last year's lecture file. Our lectures must be in a constant state of revision. This is especially true in our field of pharmaceuticals. Of the 400, plus, new drug products which were placed on the market last year, many were not definite chemical entities, but in the hands of the physician they were considered as new drugs even though they are but combinations of older therapeutic things, or a new dosage form of some standardized drug product. Our students must be able to make an intelligent differentiation of these products for the physician. The pharmacist must understand the chemistry, the pharmacology, the physiological action, and most certainly the pharmacy of every drug product.

What design should our seminars take? Or is the present pattern satisfactory? Seminars conducted in specialized areas of pharmaceutical teaching result in a stimulated and enthusiastic teacher in <u>that one particular phase</u> of pharmaceutical education. To achieve the full benefit of the seminars in the various areas, their recommendations and ideas must be incorporated with the total curriculum pattern of the college. The implementation of these ideas are frequently costly as to personnel, time, and in equipment and supplies. These in themselves might prove to be factors of limitation and a bases for discouragement of an enthusiastic teacher. However, there is another consideration still more important; namely, the task of acceptance of a specific idea by the total staff and the dean.

We need to continue our specialized teachers' seminars; but in designing our future programs, we should remember that no one area of pharmaceutical education progresses without the cooperation of the other divisions. You, for example, will leave this seminar with many new ideas which you propose to incorporate into your syllabus, but which you realize must fit the curriculum pattern of the college with which you are associated. Waiting six years to reinstitute a general seminar is, in my opinion a mistake and delays the change of implementation of new ideas from the seminars held for the teachers of specialized areas. Let us admit that it is difficult to define the limitations of one area or specialty without imposing upon another of the avenues of the educational training for the pharmacist. If we are to employ better teaching methods and develop improved curricula, then we should have general seminars scheduled every third year. I propose that these seminars be designed as an integral part of our annual meeting which should in that particular year be scheduled on a college or university campus and at a time when all academic personnel have the opportunity to participate.

If there is fault with the pattern of the specialized-area seminars, it is this--when we meet as a group of specialists, we are isolated with our fellow colleagues and are apt, because of our engrossment in our own field, to overlook or to avoid the consideration of certain of the other facets of the educational training program. This may result in a penalty, not to the teacher, but a penalty to the student.

In conclusion, may I again remind you of the primary purpose of these seminars, and then ask you if there is any way in which you as a specialist can change the pattern of the curriculum without the assistance of the other divisions of pharmaceutical specialization. Teachers in pharmacy colleges need to meet at a time when they have opportunity to consider their work and the total curriculum pattern. I am confident that as educational experts, we also operate best in an educational environment. The true objective of these meetings is to devise the best method of transmitting information from the teacher to the pharmacy student.

PHARMACEUTICAL CHEMISTRY INSTRUCTION IN GREAT BRITAIN

Arnold H. Beckett

It is first necessary to briefly review the education of a student prior to entry into a School of Pharmacy in order to obtain the correct perspective of pharmaceutical education in Great Britain.

Education before entry into a School of Pharmacy

On the basis of class performance and examination results, at the age of approximately eleven years, children, in general, are then educated at either grammar schools at which the training is of an academic character and preparatory for the universities, or in secondary modern schools where there is a combination of both academic and vocational training. There are certain safeguards to minimise the danger of incorrect student placing and provision for reallocation to protect the student who is late in developing.

At the grammar school, the student who is interested in the scientific field will study subjects such as chemistry, physics, mathematics, biology in addition to english, history, geography and a foreign language. At about the age of sixteen, the student will sit the General Certificate of Education in the above subjects at Ordinary Level, and will then proceed to specialise in four subjects in preparation for the Advanced Level examination usually taken at the age of eighteen. The training for the Advanced Level corresponds in standard to that of the first one to two years at an American University.

If the student is desiring entrance into a School of Pharmacy, the minimum university requirements for Ordinary Level subjects must be met, and in addition, passes at Advanced Level in the above examination in Chemistry, Physics, and either Botany or Zoology or Biology together with a fourth subject (preferably Mathematics at Ordinary or Advanced Level). Alternatively, the student may sit the University Intermediate Examination in these subjects - the level corresponds to the Advanced Level above.

Those who desire to take the Pharmaceutical Chemist Diploma instead of a degree, may gain entrance to a School of Pharmacy by the above routes, or via the Intermediate Examination of the Pharmaceutical Society in Chemistry, Physics and Biology (new regulations are being introduced in 1958).

Education at a School of Pharmacy

Two types of qualifications and courses for their appropriate examinations are available:

(a) Pharmaceutical Chemist Diploma This is a statutory qualification and the examinations are centrally controlled by the Pharmaceutical Society of Great Britain. (New regulations come into force in 1958.)

(b) University Degree The Universities of London, Manchester, Nottingham, Leeds, Glasgow and Cardiff offer internal degrees in Pharmacy.

A person holding a University degree in Pharmacy may become registered by the Pharmaceutical Society as a Pharmaceutical Chemist upon passing an examination in Forensic Pharmacy conducted by this Society and completing a suitable course of practical training (two years duration prior to entry for the final examination or one year's practical training in retail, hospital, or manufacturing pharmacy subsequent to entry for this examination.)

In addition to the internal degree of London University, (courses at School of Pharmacy, Brunswick Square and Chelsea College of Science and Technology) leading to the Bachelor of Pharmacy Degree, certain provincial colleges of technology, Sunderland, Bradford, Brighton train students for the external degree of London University.

Some technical colleges, Portsmouth, Plymouth, Bristol, Liverpool, Aberdeen, Edinburgh have courses for the Diploma but not for the degree in Pharmacy.

The degree course of London University is of honors standard and three years duration (equivalent to five to six years of American University when the training prior to entry into the Pharmacy course is taken into consideration.

Until 1958, the Pharmaceutical Chemist Diploma course was of two years duration but now the course has been extended to three years.

The following account is based upon conditions obtaining in the London colleges.

Degree Course: subjects studied.

In the first two years, the subjects comprise General Pharmaceutics, Pharmaceutical Chemistry, Pharmacology and Pharmacogosy; about ten hours per week is spent on the first two and five hours per week on the last two subjects. Practical work comprises about 60 per cent of the allocated time.

In the final year the student chooses two out of the above four subjects and the time is equally divided between the two chosen subjects. A dissertation is also required (exception Pharmacology) on each subject.

Degree Course: Pharmaceutical Chemistry

First two years. The lectures given are as follows, the numbers representing one hour per week of a session of thirty-three weeks per year.

Organic - (2) Because the students have already some training in organic chemistry, the more elementary aliphatic and aromatic chemistry can be covered quickly. Heterocyclic chemistry, some alkaloids and numerous medicinal agents are covered in the course.

General and Physical Chemistry - (1) Some of the physical chemistry studied in the G.C.E. course is revised. Special emphasis is given to those topics which are important in the general pharmaceutics section of the pharmacy course.

Inorganic and Analytical Chemistry - (1) (first year only)

The Practical Course involves

inorganic qualitative ..... semi-micro scale.
quantitative analysis ..... volumetric and gravimetric.
There is much emphasis on accuracy and training in techniques. Many examples of the analysis of medicinal agents and some examples of analysis of pharmaceutical mixtures are included.
organic preparations ..... a few examples.
organic qualitative ..... emphasis is given to the elucidation of structures by classical functional group investigation. Some examples of the identification of pharmaceuticals and the identification of agents in tablets and preparations are included.
Physical ..... A few experiments e.g. adsorption, rates of reaction, etc. are given and the student taught to use simple instruments such as pH meter, polarimeter, refractrometer.

Third Year. Only organic and physical chemistry is taught in the pharmaceutical chemistry course.

Organic Lectures A much more fundamental treatment than in the first two years is now given. The topics include, synthetic methods, reaction mechanisms, sterochemistry, physico-organic, basic ideas on chemotherapy. The student is trained to deal with problems of proof of structures involving data from modern physical instruments.

Physical - Lectures In addition to basic physical chemistry such as thermodynamics, much emphasis is given to the theory, scope and limitations of the use of instruments such as spectrophotometers, pH meters, polarographs, etc.

In the practical work the student is trained to use modern physical instruments and apply them to the solution of problems. The organic work involves preparative methods with special emphasis on techniques. Experiments involving chromatography, in - exchange resins, non-aqueous media titrations, chelatometry are carried out. The student is expected to use U.V. data, potentiometric titrations, polarographic data, etc. in the identification of unknown compounds.

The above course obviously is integrated with topics taught under the heading of pharmaceutics and pharmacology.

(Pharmaceutics - in the third year work, microbiology and the problems involved in the formulation and stability of products receives much emphasis. Detailed attention is given to the use of instruments in the iatter topic.

Pharmacology - the third year work includes quantitative biochemistry and pharmacological assays of drugs.)

In the third year the student is also trained in Literature work to enable him to produce the dissertation required.

Pharmaceutical Chemist's Diploma

At present, this course is not too dissimilar from the first two years of the degree course but the emphasis is less fundamental, less attention, for instance, is given to the theoretical principles of organic chemistry.

College and Student Finances

College - The fees paid by the student contribute only a negligible part to college expenses. The grant comes from the Government (via the University Grant Commision in the case of the Universities) or from the Government and the local authority (town or borough) in the case of the Colleges of Technology. Provision is made for post-graduate as well as undergraduate work.

Student - In general, most students receive grants or scholarships from Government agencies or local authorities which cover not only their tuition fees but much of their living expenses. For post-graduate work, certain scholarships are also made available by industry.

A director of research work in a British college does not have to spend so much of his time trying to raise money for research as does his American counterpart.

Ph.D. in Pharmaceutical Chemistry and Post-Graduate Work

A Ph.D. student in Britain does not have formal course work as in America. The Ph.D. course involves research work and the presentation of a thesis but the student is expected to increase his knowledge in areas not directly covered by his thesis.

The duration of the course is approximately three years.

There has been a great increase in research work in Schools of Pharmacy during the past few years but unfortunately only few of the schools are yet involved to a significant extent.

The paper on "Sterochemistry and Mechanism of Action of Synthetic Analgesics" illustrates how the training in the Bachelor's Degree course is applied and extended in post-graduate work in one of the topics under investigation at Chelsea School of Pharmacy.

Employment of Pharmacists in Britain

The majority of students obtaining a good degree (first or second class honours) at the London Colleges obtain posts in the pharmaceutical industry or the larger hospitals.

Those who take the Pharmaceutical Chemist Diploma usually obtain employment in retail pharmacy.

Those who obtain the Honours Degree find employment in industry in pharmaceutical development, pharmacology, analytical, food and drug analysis, administration, etc. For the more senior positions a Ph.D. Degree is becoming essential.

Increasing numbers of pharmacists with a Ph.D. Degree are being employed in research especially in the fields of pharmaceutical development, medicinal chemistry and pharmacology. This is a recent development which arises directly from the introduction of the Honours Degree of London University in 1949. The new training enables a student to proceed directly to his Ph.D. without the necessity of taking further courses as had previously been necessary. Other authorities are realising the value of training received by a pharmacy student at the bachelor and doctorate level.

The great changes that are occurring in the scientific level of pharmacy are undoubtedly a direct result of the improved standards in the schools of pharmacy and the increase in emphasis on research in the schools. Prior to 1950, a few teachers in Schools of Pharmacy had a Ph.D. Degree; now a Ph.D. for a teacher is becoming the rule rather than the exception.

Undoubtedly, the scientific side of pharmacy in Britain is gaining increasing recognition and prestige amongst those who work in other scientific disciplines. We can look to the future with confidence because the design of our degrees in pharmacy is sound and the calibre of those who teach in these courses is good.

Monday Session

Ole Gisvold

Chairman

PHARMACEUTICAL CHEMISTRY INSTRUCTION FOR PROFESSIONAL PHARMACEUTICAL SERVICES.

Harry W. Hind

The three main areas of professional activity which are indispensable to the responsible practice of retail, hospital, detail, and industrial pharmacy are as follows: (1) Organization of pharmaceuticals; (2) consultation with the physician, and (3) formulation for dispensing. I shall attempt this morning to outline the application of pharmaceutical chem istry to these professional functions.

We are all aware of the dynamic nature of our pharmaceutical industry. I believe it is to the everlasting credit of the drug industry that year after year five to ten per cent of its gross sales volume has been allocated to research programs of various kinds. In 1957 this amounted to approximately 125 million dollars. The result has been a tremendous flow of new drugs which all of us have witnessed. We have seen drugs become obsolete after short term use. How many drugs introduced only ten years ago are still in use? Surveys show that the mortality rate is approximately 80%. Cortisone, for example, first introduced in 1950, was largely replaced by hydrocortisone in 1952. Improved corticosteroids began to appear with the fluoro- derivatives in 1954, prednisone and prednisolone in 1955, triamcinolone in 1956, and methylprednisolone in 1957; and the latest of the series, hexadecadrol, just recently announced by Merck, is reported to be 30 times more effective than hydrocortisone. In other areas of medicine similarly dramatic changes have occurred; the antihistamines, tranquilizers, antibiotics, and diuretics are only a few among a long list of abvious examples. "Miracle Drugs" is not only the name of a Wilshire Boulevard drug store, it is a significant expression of the commanding role of drug therapy in the modern m anagement of just about every kind of illness.

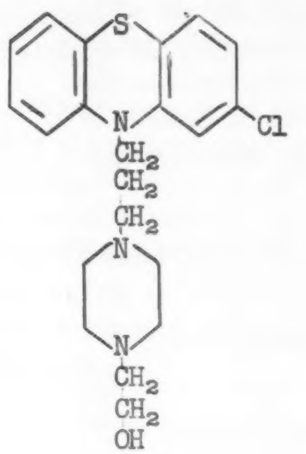
(But the inevitable corollary to scientific advance is increasing technologic complexity.)

The modern physician is overwhelmed by m ore than joy at the broad range of therapeutic agents available to him. If he has been out of medical school ten years, ten times many hundreds of new products have appeared on the market. Of those which he studied in medical school only 20% are still in use. The physician would have to devote full time to the evaluation of new drugs appearing daily on the market, but he cannot do this. His alternatives are (1) to throw up his hands at the pharmaceutical profession and continue his practice using only those drugs with which he is already familiar, or (2) to form the habit of consulation with a reliable pharmacist.

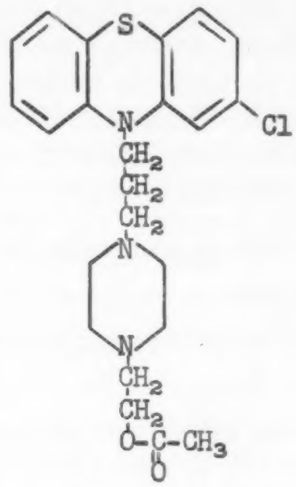
The pharmacist is the logical member of the medical team to serve as consultant to the physician on new drugs. If he cannot fill this need and discharge this obligation, he cannot hope to establish him self as a professional man. Of what will this consultation consist? It is certainly not sufficient that the pharma-

cist should be able merely to remember the trade name of a drug, the name of the company which manufactures it, and the purpose for which it is used. Information at that level is the property of every housewife in these enlightened days. The physician lacking the proper background does not have the ability to correlate trade names, generic names, and chemical structure with pharmacologic activity. It is this aspect of the pharmacist's function that I wish to emphasize at this time. It is a responsibility which has been neglected by the profession at large. If the pharmacist is ever to perform his appropriate function in the physician-pharmacist relationship, the pharmacy student must be given a sound basis of training in pharmaceutical chemistry and the biological sciences through pharmacology and toxicology. To illustrate this principle I will discuss for a moment certain phenothiazine derivatives now commercially available which have tranquilizing properties. The trade names of these drugs, which are currently being dispensed in vast quantities by pharmacists, are: Sparine (Wyeth), Thorazine (SKF), Vesprin (Squibb), Compazine (SKF), Dartal (Searle), and Trilafon (Schering)

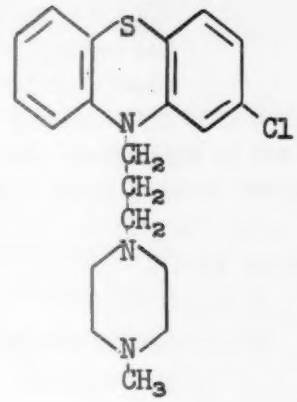
PHENOTHIAZINE DERIVATIVES



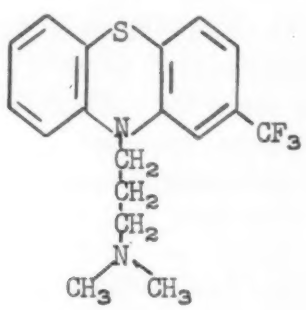
TRILAFON (Schering)
perphenazine



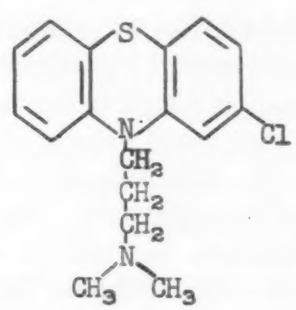
DARTAL (Searle)
thiopropazate



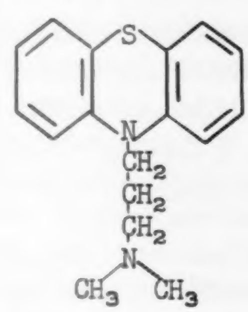
COMPAZINE (S.K.F.)
prochlorperazine



VESPRIN (Squibb)
triflupromazine



THORAZINE (S.K.F.)
chlorpromazine



SPARINE (Wyeth)
promazine

Slide 1 shows, the trade, generic names and the chemical structure of the phenothiazine derivatives just mentioned. A properly trained pharmacist will be able to ascertain the following useful facts concerning these compounds by a comparative study of their chemical organization.

1. They are phenothiazine derivatives.
2. The difference between Vesprin, Thorazine, and Sparine is the substitution on the 2 position of the phenothiazine ring
3. Trilafon, Dartal, and Compazine differ in the substitution on the piperazine ring.

4. The tranquilizers have the amino group substituted on the gamma (3) carbon of the side chain, whereas the antihistamine and antispasmodic drugs of this series have the amino group substituted on the beta carbon (2). Example: Phenergan (Wyeth), used as an antihistaminic, and Parsidol (Warner-Chilcott), used as an antispasmodic, are both substituted in the beta position.

5. Compounds having the highest molecular weight in the series are the most active therapeutically.

6. These drugs differ with respect to their physical and chemical properties.

7. The basic nitrogens of the amino and piperazine groups form acid salts.

8. Dartal would probably be subject to hydrolysis because of esterification, whereas the others would not.

In addition to the information which can be obtained from an examination of the chemical structures of these compounds, the pharmacist should possess general information about this popular group of drugs to enable him to place the phenothiazines in their proper class of the four main groups of tranquilizers, namely: (1) the phenothiazines (as shown); (2) reserpine alkaloids; (3) diphenylmethane derivatives, and (4) the substituted propanediols. He should also know that the phenothiazines, like the diphenylmethane derivatives and reserpine, act on the autonomic nervous system, whereas meprobamate depresses the central nervous system. Dosage, dosage forms, cautions and contraindications are likewise important to the pharmacist's knowledge of these drugs.

I hope that this example illustrates the application of pharmaceutical chemistry to the responsible daily practice of retail pharmacy as well as the necessity for a sound knowledge of pharmacology and toxicology, physiology, anatomy, and physical chemistry. A further example from my own experience may be even more to the point.

Prescriptions which pose physico-chemical problems of incompatibility and stability frequently appear upon the counters of retail and hospital pharmacies. It is the pharmacist's duty to recognize and solve such problems. One such difficulty arose not long ago when a new use for epinephrine was reported in the treatment of glaucoma. Physicians had been directed to request that the drug be dispensed in a borate buffer of pH 8.0. As you know, epinephrine undergoes oxidative change at this pH and changes color. We received a number of inquiries from pharmacists. We explained to them the relationship between epinephrine stability and hydrogen ion concentration, and recommended the following vehicle:

Boric acid	20 gm.
Chlorobutanol	5 gm.
Sodium Bisulfite	3 gm.
Distilled water, q.s. ad	1000 cc

Epinephrine hydrochloride dispensed in this vehicle is chemically stable, physiologically active, and not irritating to the tissues of the eye.

The pharmacist may expect to be confronted with similar problems at any time. Only if he has come away from pharmacy school with a thorough knowledge of the physical and chemical properties of drugs can he deal with this type problem which is bound to rise in his daily practice. Unfortunately, the great majority of our present day retail pharmacists have not received adequate scientific training so as to function as informed consultants and competent dispensers. Such individuals cannot realize the opportunities lost in strengthening physician-pharmacist relationship.

I should like to urge those of you responsible for teaching fundamental science in a school of pharmacy to constantly remind the student of the applications of the discipline for which you are responsible. It has been my observation that a large proportion of pharmacy students regard their basic science courses as so many arbitrary hurdles thrown across their path in the course of attaining their professional objective. By showing how the basic sciences serve these objectives, the student will take a healthier attitude and your teaching will be much more effective.

In the foregoing I have been dealing exclusively with the special problems of retail and hospital pharmacy. The two remaining areas of interest to graduating pharmacists are detail pharmacy and industrial pharmacy.

Pharmaceutical salesmanship is a perfectly acceptable career for a talented graduate of pharmacy school and offers many satisfactions. It too has its responsibilities. Most doctors recognize the value of the information they can obtain in just a few minutes from the detail man waiting in his outer office. But the physician learns to distrust and resent glib and extravagant claims based on insufficient understanding of the technical factors involved in choosing drugs for therapeutic use. It has been our experience that success in detail pharmacy is dependent on good scientific training, and that those pharmacists serve the industry best who are equipped to combine sound technical discussion with the routine blandishments of salesmanship.

At any other time I would have enjoyed the opportunity of developing the subject of industrial pharmacy in some detail. Perhaps fortunately for us all my task has been greatly simplified with the appearance of the June issue of the Practical Edition of the Journal of the American Pharmaceutical Association. This issue is devoted entirely to the subject of industrial pharmacy. These articles constitute an excellent review of the field, and there is little more that I need do than commend them to your attention. However, a few points may deserve emphasis here.

The training required by the pharmacy student who wishes to enter industrial pharmacy is the same as for the student desiring to make his career in the professional areas already discussed. The principal difference between industrial pharmacy on one side and retail and hospital pharmacy on the other is the opportunity to specialize. Pharmaceutical companies tend to restrict their product

development to certain types of drugs. The type and degree of the pharmacist specialization will depend upon the interests of his firm and the area of responsibility within the firm to which he may be assigned.

One problem which may confront the pharmacy graduate who wishes to enter the exciting field of industrial pharmacy is that the industry as a whole is not well informed concerning the technical qualifications of our best graduates. I talked recently with an executive of a large pharmaceutical company and came away with the impression that he was completely unaware of the modern pharmacy curriculum. Becuase of this he had never given serious consideration to the college of pharmacy as a source of trained personnel. I urge all educators and administrators to undertake a job of public relations with the drug industry and to bring to the attention of recruitment executives the qualifications of the modern pharmacy graduate. Industrial pharmacy should represent a major area of employment for our graduates.

In summary, pharmaceutical chemistry is an indispensible discipline for the understanding and operation of the drug industry and the profession. Pharmaceutical chemistry is an applied science and essential for an understanding of therapeutic agents. As such it should be remembered that its development requires thorough training in the fundamental disciplines of chemistry, physics and biology. If you wish to turn out students well trained in pharmaceutical chemistry they must first receive sound training in the basic sciences that precede. The level of achievement and development of pharmaceutical chemistry is largely dependent on the quality of instruction in these fundamental sciences and if this is true, perhaps these basic disciplines should receive more careful consideration in the pharmaceutical curriculum.

The pharmacy student must approach these basic science courses with a full understanding of what he must take with him into the future.

THE UNDERGRADUATE PHARMACEUTICAL CHEMISTRY CURRICULUM AND ITS PREREQUISITES

George L. Webster

You have just been told by a practising pharmacist a number of reasons for devoting a substantial amount of time and effort in the curriculum in Pharmacy to pharmaceutical chemistry. It seems to me that this is the proper note upon which to open a seminar on the teaching of pharmaceutical chemistry for, it is most encouraging to the devotees of a discipline to be told that the ultimate user of their product find it important. I would like to thank Mr. Hind for his encouraging remarks.

It is my purpose to bring into focus for a few minutes the generalities of the curriculum in Pharmacy, as pharmaceutical chemistry and its underlying basic sciences are related to it. Mr. Hind has noted a number of applications of chemistry to Pharmacy as it is being practised. It seems pertinent to examine how our teaching of basic and applied chemistry should provide the understanding which makes it possible for our graduates to perform adequately in the present and to grow along with the inevitable widening of the applications of chemistry and physics to Pharmacy.

A reasonable generality with which to begin is one which proposes that, as a result of a properly organized sequence of courses, the pharmacist should have an understanding of the nature of most of the substances currently being used in medicine and in the household and sufficient training in the reasoning process to enable him to grow in understanding with future developments.

It is necessary to particularize, under this generalization, in order to be able to evaluate our present and future practices in curriculum building.

Almost any type of chemical substance has been or may be used in medicine either because it alters physiological activity or because it may act as a carrier, solvent, diluent, adjuvant or antidote for an active substance. The beginning of understanding of pharmaceutical chemistry is an understanding of chemical principles and laws.

The weight of experience in teaching has recommended that a student's first introduction to chemistry should begin with a study of the elements and the periodic table. At one time inorganic chemistry recommended itself as the starting point because of the assumed simplicity in the behavior of elements other than carbon. As the gaps in the periodic table were filled in and more information accumulated regarding the energetics of supposedly simple atoms, the assumption of simplicity became untenable. However, it is still possible for a beginning student to obtain a general introduction to chemical theory and laws using examples drawn from inorganic chemistry and qualitative analysis.

In all of the proposed extended curriculums in Pharmacy that have come to my notice, the faculties in the colleges of pharmacy are expecting their students to obtain their first introduction to college chemistry in a standard course in General Chemistry and Qualitative Analysis. In nearly all cases, these courses are administered by departments of chemistry outside of the colleges of pharmacy and must be presumed to be directed to the teaching of fundamental principles. This I believe to be desirable. The acceptable course should not carry less than 8 semester hours of credit and optimally should comprise 10 semester hours.

The above circumstance makes it imperative that the curriculum in the college of pharmacy provide for an applied course which will require the student to become familiar with the chemicals with which he can reasonable be expected to be familiar as a pharmacist. Many of the better courses in General Chemistry and Qualitative Analysis do not offer opportunities for the student to study the chemicals. The necessity for a descriptive course in inorganic chemicals and their dosage forms cannot be denied. What has been argued is the question of a proper title and administrative responsibility. Since it obviously must be taught in the College of Pharmacy, the assignment of the subject matter to the department or professor most competent to teach the course should be the responsibility of the faculty of the college.

Inorganic Quantiative Analysis may be taught satisfactorily either in a College of Pharmacy or in a preprofessional curriculum outside of the professional college. The advantages to the student in acquiring the precision techniques of quantitative analysis at an early period are too obvious to need much emphasis. A standard course is recommended rather than one combined with Drug Assay which should come later, after Organic, Physical and Biological Chemistry have been completed.

Organic chemistry also takes its place among the fundamentals of pharmaceutical chemistry. The nature and extent of the course treatment is about as variable as are courses in General Chemistry. Many curriculums where the graduates are not expected to have a thorough understanding of organic chemistry are content to provide only a superficial knowledge. Since such curriculums attract many more students than are engaged in the study of Pharmacy and Chemistry, a student who transfers from a Junior College or after two years in a college of Liberal Arts and Sciences may have been advised to enroll in an inadequate basic course in Organic Chemistry. For this reason, many of the extended curriculums which accept two years of college for entrance upon the professional years prefer to schedule Organic Chemistry in the first year of the professional curriculum rather than be plagued by the problem of trying to supplement an inadequate basic course.

The necessity for a rigorous course in Organic Chemistry for the pharmacist is too well established to need much emphasis in this company. The fluctuation of interest, from decade to decade, between the organic chemistry of natural products and synthetic chemistry serves only to emphasize the desirability of better understanding of the fundamental laws and theories of the science.

A recent proposal was made in our faculty that since an adequately taught course in Organic Chemistry included the chemistry of carbohydrates, proteins and fats as customarily taught in the first half of standard courses in biological chemistry, there seemed many reasons why the Department of Biological Chemistry should concern itself only with the chemistry of the metabolism and utilization of these materials. We saw in this a way of avoiding unnecessary repetition and consequent saving of time in class which the student might spend in study.

A standard introductory course in college Physics preceded by at least one year of college Mathematics has seemed to me to be fundamental to Pharmacy for so many years, it is almost incredible that there should be even one college of pharmacy in the United States in which this fundamental science was alloted only one semester in the first year and a presumed (by me) prerequisite mathematics course was scheduled in the fourth year of the curriculum. One has only to casually review the professional and scientific activities of the curriculum in Pharmacy or of a practising pharmacist to evoke numbers of uses of the principles of Physics. Since the practice of pharmacy in hospitals is a growing challenge to our graduates, it seems inexcusable if we allow them to acquire their knowledge of radio-isotopes in medicine or in military science from the public press rather than from a trained physicist.

When one speaks of the principles of Physics as being fundamental to the professional activities of Pharmacy, one must, of necessity, recognize that college mathematics up to and including Analytical Geometry and introductory Calculus is also fundamental. Resistance to mathematics as a required subject is probably more widespread than to any other suggestion. At the same time the "practical" pharmacists bemoan the so-called "fact" that our graduates frequently fail on arithmetical problems I submit that the mind that can understand and visualize a problem which he can solve algebraically or graphically or by the calculus does not have trouble with problems of dilution, concentration or discounts. Conversely, the mind that refuses to concentrate on fundamental mathematical problems because they are "not practical" belongs to the same student who in later practice uses an aspirin tablet for a five grain weight.

A similar resistance developed when the recommendation was made to require at least one course in what was generally labeled Physical Chemistry. I have a personal theory on this, that the resistance arose because of the experiences some of us had with Physical Chemistry when we were students. From the vantage point of some additional years, I am now convinced that most of my personal indifference to Physical Chemistry was sponsored by the attitude of most organic chemists of that time which was to the effect that Physical Chemistry was "impractical." I freely admit that I have lived to regret my deficiency.

Chemistry teachers of today have a great asset when they advise the inclusion of Physical Chemistry in the curriculum of Pharmacy. Product development, product stabilization, absorbability and availability of difficultly soluble drugs, solubilization, dispersion, instrumental analyses and many other very "practical" problems of pharmaceutical practice are solved by the applications of physicochemical principles. Presumably, these problems could be solved, given sufficient time, by trial and error

but they had not been solved by even the ancient "great ones" of Pharmacy who lived before the development of Physical Chemistry. I recommend then, that every pharmacist who graduates be indoctrinated with the method of thinking which is characteristic of Physical Chemistry. If this has to be made more attractive by naming it Physical Pharmacy, I raise only mild objection as a matter of principle. My great concern is that the course by either name ought to be fundamental in its approach for at least one term, followed if desired by another course in applied Physical Pharmacy.

I have great regard for fundamental courses because I have observed that while new break-throughs in understanding continue to be made which enlarge the basic fields of physics and chemistry, much progress and most of the useful applications of science are made by those who are thoroughly grounded in fundamentals. The clever new dosage forms are adaptations of fundamental principles of chemistry or physics applied to some chemical which someone else has developed by applying and adapting a different set of theories and facts.

The applied courses which can be labeled Pharmaceutical Chemistry should be designed to test the understanding and the ability of the student to apply general scientific principles to new situations. These courses come late in the curriculum and afford rewarding opportunities for both students and professor to analyze and project -- analyze the relationship of existing compounds or methods to theory, to older compounds or methods and project on the basis of modern knowledge and theories what is likely to be available in that future time when the student will be in his prime as a pharmacist, a teacher, a medical service representative or a research worker.

There are only two titles which I suggest for these applied courses. I have used them before so they will come as no surprise. They are: (1) Drug Assay, in which I suggest that a great deal of revision of existing manuals can profitably be done and (2) the Chemistry and Pharmacy of Medicinals.

You will listen to detailed syllabi of these courses under these or other titles later in the Seminar. I know we will profit by the suggestions to be made.

In our discussions during this Seminar, we may speak as if we were planning a curriculum in Pharmaceutical Chemistry. I know most of you who are members of the faculty of a College of Pharmacy well enough to know that you do not actually restrict your thinking as narrowly as might be suspected from the presentation. This group, I am sure, is fully aware that the basic courses in Chemistry are fully as useful to the other disciplines that make up Pharmacy as they are to the succeeding courses in Chemistry. Thus Inorganic, Organic and Quantitative Analysis are important to Pharmacy, Biology, Biological Chemistry and Pharmacognosy; Physiology, Microbiology, Pharmacognosy and Pharmacology are benefitted by Physical Chemistry and Biological Chemistry; Dispensing Pharmacy and Pharmacology draw much of value and interest from Drug Assay and the Chemistry and Pharmacy of Medicinals.

A final note must be made about the importance of prerequisite, basic science courses to graduate study. I have been depressed too often by the spectacle of an alert, ambitious graduate of a college of pharmacy presenting himself for graduate study and unaware until this moment that his college had handicapped him by lack of insistence upon adequate basic science courses. In the extended curriculum plans, I sincerely hope that this regrettable situation will be corrected.

DISCUSSION

Dr. Smissman questioned the teaching of basic carbohydrate and protein chemistry in the organic course rather than a biochemistry course. Dr. Webster agreed that comprehensive coverage of these subjects probably would not be possible in either course, but probably would require a special course in the chemistry of natural products. Adequate coverage may be possible in the organic course required for pharmacy students, especially if it be increased from eight to ten semester hours, and if the organic course be followed by a course in biological chemistry dealing with metabolism of carbohydrates, fats, proteins, etc. Plans along these lines have been approved by the biological chemistry department.

Dr. Smissman challenged the implication that students trained in mathematics through calculus would not require a course in pharmaceutical calculations. He supported his opinion that a special course is required on the basis that "the type of work that they get in their math course does not give them the know-how to work these pharmaceutical calculations." Dr. Webster pointed out that "pharmaceutical chemistry is taught largely by methodology rather than by understanding." Allegation is a methodological approach based on algebra and it may "be even better for you to quit teaching it and to teach them how to solve this problem by algebra."

Dr. Boblitt commented that many of the difficulties could be resolved if teachers in colleges of pharmacy were better trained in higher mathematics, physical chemistry, etc.; and if they had better textbooks, with adequate theoretical presentations at their disposal.

Dr. Martin suggested that the many prerequisites in the curriculum prevented specialized training in areas of pharmaceutical endeavor early enough in the undergraduate program. Dr. Webster pointed out that the program allows for sufficient training in fundamentals and also adequate freedom for specialization in the undergraduate curriculum. Specialization must not be achieved, however, at the expense of fundamental training. Dr. Martin stressed the importance of calculus as a prerequisite for "good solid" course in physical chemistry. Dr. Webster replied that such a course should be elective, but that an introductory course would be essential for all students. The final two years provide the opportunity for students to specialize, e.g. to enroll for more basic science courses instead of courses in business administration if the student is contemplating graduate study. Courses will be

available that are of special interest to future hospital pharmacists, medical service representatives (pharmacology, physiology, or business administration), etc. The opportunity for basic training and specialization without exceeding loads of 16 credits per semester is the great advantage of the extended curriculum.

Dr. Stuart asked for clarification on the teaching of organic chemistry in the third year rather than in "Junior Colleges". Dr. Webster pointed out that students presenting only two years of college for admission to the College of Pharmacy will often have inadequate training in organic chemistry, e.g., courses designed primarily for pre-medical students. On this basis, organic chemistry should be given in the first professional year of the 2-3 curriculum. Dr. Stuart reported that a full year of organic chemistry would be required for admission to Oregon State College, School of Pharmacy, to provide the necessary preparation for modern courses in pharmacognosy, pharmaceutical preparations, organic medicinals and pharmacology.

Dr. Beckett stressed the importance of training in gravimetric methods of analysis in preparation for other courses in the curriculum. He also indicated that mathematics courses such as algebra and calculus trains a person's mind while mathematical manipulations in pharmacy provides training in accuracy.

SYLLABI OF INORGANIC PHARMACEUTICAL CHEMISTRY COURSES--THE INORGANIC CHEMIST'S APPROACH

Clarence A. Discher

Before discussing my topic for the morning, it behooves me to clear the air a bit. I feel much as "Christine Jorgenson" must have felt when among women before her famous operation. The program says that my discussion is to be from the point of view of an inorganic chemist. Let me confess, it will be impossible to keep the point of view of the teacher out. However, an even greater deviation from the point of view expected will probably result from the thorough brainwashing I have undergone at the hands of my pharmacy colleagues of the past eleven years at Rutgers.

There are three areas for discussion, which I will name before considering each in turn. First, one must consider the nature of the objective for the Inorganic Pharmaceutical Chemistry courses. Second, we will review the various problems which beset the teacher in the field. Finally, we will consider syllabi which I sincerely believe achieve the objective and, at the same time, meet the teaching problems as well as possible.

Objective

To me, there is a single objective in teaching Inorganic Pharmaceutical Chemistry: To give as broad as possible an understanding of the chemistry of inorganic substances of importance, or possible importance, to an individual in any of the pharmaceutical fields. Although receiving my undergraduate training in Education (with the capital E), you will note that I do not propose to dissipate my energies in teaching toward those high-sounding objectives the Educator so dearly loves, i.e., educating the whole man. I am a firm believer that the most important element in the success of an individual is a thorough understanding of the work which he is doing.

To avoid being misunderstood, let me also point out what is meant by "understanding of the chemistry". I mean nomenclature and thorough study of physical and chemical properties of substances. This does not include those substances and topics which have only a general interest to pharmacy, such as uranium hexafluoride, and the metallurgy of aluminum. These should be included in the pre-pharmacy portion of the curriculum.

It should also be noted that this objective implies explicitly that emphasis is to be placed on the descriptive aspects of inorganic chemistry--not the theoretical.

Problems

The achievement of the objective set forth is beset by some rather serious problems. These problems must be recognized and overcome when possible if successful teaching in the field of inorganic pharmaceutical chemistry is to be achieved.

The first of these problems is one which is quite out of the hands of the teacher in our field, at least in a direct sense. It is the background preparation of the student. There has been a tendency over the past two decades to include more and more theory in General Chemistry. Since the time devoted to General Chemistry has remained unchanged, this has been done at the expense of the descriptive chemistry of the elements and their compounds. Early textbooks for the beginning course were largely descriptive chemistry. Today, an average textbook devotes about half of its pages to this still important aspect of chemistry. I take the position, as an inorganic chemist teaching Inorganic Pharmaceutical Chemistry, that theory has its place, but its proponents, like the educator who would teach educational theory to the exclusion of subject matter, forget that for practice theory can be over-emphasized. In its present state, theory alone cannot come up with the answers to much of the chemical behavior of interest in pharmacy, the practitioner must know the descriptive chemistry of the substances with which he is working.

There has often been still another unfortunate trend which has further decreased the time a general student devotes to descriptive chemistry of the elements and their compounds. It is the deplorable inclusion of Qualitative Analysis in the second semester of General Chemistry. This not only reduces the time available for descriptive chemistry, but, too often, relegates Qualitative Analysis to a practically useless scheme. There is too little time available in such a combined course to take advantage of the teaching opportunities which exist for the study of the properties of the substances covered in the qualitative scheme.

Both of the problems just discussed are probably tied to the scarcity of men trained in inorganic chemistry who are available for the teaching of General Chemistry. Too often, the only descriptive chemistry of all of the elements the instructor in charge of the course has had is that which he is trying to pass on to his students. The tendency, under these conditions, is, unfortunately, to omit entire portions of this aspect of chemistry with, "It is not important". I've often quailed on seeing some of the fundamental descriptive chemistry that has been shrugged off in this manner.

There is still another background problem that has confronted more and more of us in the past few years This is the inclusion of General Chemistry in the pre-pharmacy curriculum. In the Arts and Sciences School, the course must be presented from a most truly general point of view because of the broad variation in the objectives of the students in the class: chemistry majors, chemistry minors, pre-pharmacy, pre-dental, pre-medical, biology majors, and students merely fulfilling a science requirement. This means that many aspects of chemistry are included in a very superficial way. On the other hand, when only pharmacy students are in the class, many of these superficially covered subjects, i.e., biochemistry, may be omitted entirely. They will be covered more adequately in a later course. The time saved in this way can be spent in giving the student a better background in some of the aspects of chemistry he needs, but which will not be taken up elsewhere in his curriculum. Unfortunately, there is not much to be done about this. If more than one General Chemistry course is offered by the Chemistry Department, the problem can be minimized by having the pharmacy students take the more rigorous course.

So much for the background problems. There is an even more important group of problems which, fortunately, is under our direct control. These are the problems which are inherent in the Inorganic Pharmaceutical Chemistry course itself. The first of these is the encyclopedic nature of much of the material to be covered. One has only to open one of the textbooks in the field to realize this. For good teaching, this encyclopedic nature must be reduced as much as possible. A second problem is to be faced in the organization of the course. Shall it be based on the cations, the anions, or what have you? An answer is given in the next section of this paper. The third of the problems arises from the fact that most of the compounds studied are electrostatic in character. This further complicates the order of presentation since in compounds, the cation cannot be separated from the anion--both are there despite anything you may try to do.

A third group of problems are those which are related to the pharmacy curriculum. One must consider the place of theory in Inorganic Pharmaceutical Chemistry. My position has been that theory, i.e., the quantitative aspects of pH, buffers, isotonicity, theory of solutions, is generally best covered in other courses, preferably physical chemistry, or if one wishes to get into semantics, physical pharmacy, or any other name. For instance, at our school, this material is covered in our third-year course, Pharmaceutical Preparations.

Time allotted can be a serious problem, as it is at our college. Two hours for one semester is totally inadequate. It did my morale good to hear Dr. Shinkai, who taught our course this year, complain bitterly about lack of time for adequate coverage of essential subject matter.

Overlap with Organic Pharmaceutical Chemistry can be a problem. Generally, this is not serious since the active or important group can be taken as the point of departure.

Finally, there is an unfortunate psychological problem which should not exist. Because of the publicity and predominance of work in the organic field, too often the feeling of the students (and sometimes of people who should know better) is that Inorganic Pharmaceutical Chemistry is unimportant. The instructor must constantly be doing missionary work. I like to challenge those who think that organics are the means to all ends to synthesize a substitute for the iron of hematinics. Or I like to call attention to some fine examples of recent work, such as that by our Professor Iannarone, who has shown that iodine is an excellent antibacterial, a fact so often overlooked in our preoccupation with the organic antiseptics.

Course Organization

The question now arises as to the nature of the topics to be included in the Inorganic Pharmaceutical Chemistry course. First, and most important, a good background in the descriptive chemistry of the elements and their compounds must be developed. This should include some work with the less familiar elements and compounds, which can be accomplished by a well rounded understanding of the interrelations of properties existing within families of elements. Also to be included should be the chemistry of special types of compounds or reactions important in Inorganic Pharmaceutical Chemistry, i.e., antacids and antacid action. Finally, this course is the only logical place for the inclusion of a background in radio-chemistry.

The question of whether or not laboratory work should be included in the course as a teaching tool is a difficult one to answer. It must be decided on the basis of the time allotment and the scope of course desired. In our present course, at Rutgers, we do not have the time for a laboratory. However, I will discuss a proposed program which would include a laboratory later.

Having decided the type of material to be included, a decision must be made as to the best method of presentation of this material. My preference is a course organized on the basis of periodic classification. Both of the textbooks in the field claim to follow periodic classification, but lapse from it largely because of following the older Mendeleev form of the table rather than the long form. I insist on the long form because otherwise the transition elements are treated with the typical elements. This adds unnecessary confusion to the course. Also, the last row elements should be treated as a rare earth series starting with Actinium, rather than as presented in the older tables, i.e., including Uranium in the Group VI typical elements.

Use the periodic classification in teaching Inorganic Pharmaceutical Chemistry gives certain very definite advantages. Taking advantage of group properties in teaching greatly reduces the amount of encyclopedic work. It makes possible the covering of most properties of the compounds on the basis of group behavior, thus reducing specific encyclopedic learning to the exceptions to group behavior.

Periodic classification has a further advantage, important from the time element. It makes it possible to cover only lightly those elements and compounds of minor importance, since their properties can usually be predicted reasonably well from group relationships. This is especially important since new uses and revival of old uses of inorganic compounds is continually taking place.

Certain other relations exist in the periodic table which can simplify teaching: There is the metal-nonmetal grouping within the table. There is the tendency for the first row elements to depart from group behavior more frequently than others--which fact can happily be simplified by use of the bridge element concept of the periodic table.

Teaching strictly on the basis of periodic classification can, at first glance, seem to exaggerate the problem of the ionic makeup of most of the inorganic compounds studied. However, within limits set up in the section of this paper dealing with order of presentation, this problem can be minimized and the properties of the respective cation and anion can be covered, without serious deviation, within their respective groups. It grieves me to have the chemistry of an element, i.e., boron, scattered about in three or four different places.

The problem of the ions is best minimized by judicious development of the order of presentation and by impressing upon the student that the properties of an electrovalent substance are the summation of the properties of its constituent ions, within limits. One must keep in mind, however, that simple summation is not always the rule. For instance, while the properties of sodium chloride are largely the sum of the properties of the sodium ion and chloride ion, the same cannot be said about the solubility behavior of silver chloride. The best analogy is that from genetics. As with the genes, you may think in terms of dominant and recessive characteristics of the ions.

We are now ready to build up a course outline for Inorganic Pharmaceutical Chemistry. Obviously, one must begin with a discussion of periodic classification. This is best followed by a discussion of hydrogen, water, and hydrogen peroxide. The decision must then be made as to which group of the periodic table should be studied first. I favor the alkali family (including the ammonium ion) because, here, we have very well defined group behavior, with strongly characteristic cations whose important properties can very easily and adequately be covered by the study of a minimum number of salts. Only a few anions need by covered concommitantly to give the necessary background for a good understanding of the properties of salts from this group. At this time, I would have the student study the alkali salts of the following anions: oxide and hydroxide, carbonate and bicarbonate, sulfate, and the organic anions--acetate, tartrate, citrate, and lactate. These anions in themselves are very characteristic and generally their stability and properties are such that covering them at this time rather than with their respective families raises no particular problems. They provide, for study, salts with a sufficiently representative range of properties to adequately bring out the properties of the alkali cations.

The remaining families would be covered in the following order:

Alkaline Earths
Halogens
Groups IB and IIB
Typical elements of Groups III-VI, inc.
Transition Elements
Inert Gases
Radiochemistry

Only the salts of the anions (or cations) already studied at the time a given family is taken up would be covered at the time. For instance, sodium borate is not studied until Group III because the properties of interest in this salt are not due to any peculiar behavior of the sodium ion, but rather are due to the properties of the borate ion.

It should be noted that the typical elements have been separated from the transition elements of a given group, the transition elements being covered as a family. Except for the behavior in their highest valence state, the transition elements do not generally exhibit the behavior of the so-called typical elements of these groups. Rather they have properties which are peculiar to the transition elements as a family, i.e., color, highly variable valence. By grouping them together in this way, one can take advantage in teaching of the prominent horizontal family similarities, especially in the lower valences.

Having developed the method of presentation and an overall outline a typical group treatment can be outlined. The following items would be considered on a group basis: The electronic structure of the elements involved would be developed and used to show the possible valence(s) and the kinds of valence possible. This would be followed by a discussion of group properties. First, such physical properties as solubility behavior, color, and items of special interest in the particular family would be considered. This would be followed by a thorough study of

the chemical behavior of the group under the heads, acid-base properties (including amphoterism when present), oxidation-reduction properties, and complexation behavior of the family. Physiological chemistry of interest would be included, but on a limited scale because of the inadequate background of most students in this branch of chemistry at the time they take Inorganic Pharmaceutical Chemistry.

The work on a given family would then turn to consideration of the specific elements and their compounds. The items selected for coverage would be official compounds, official preparations, substances not official but having frequent appearance in pharmaceutically important preparations, and possibly some important analytic reagents.

The discussion of a given substance would, of course, vary. However, in general, the following items would be covered. A student would be expected to be proficient in nomenclature--official name, chemical names, common names, and latin name if markedly different from these. A review of how the substance under consideration obeys family properties would be followed, when necessary, by a discussion of those ways in which it fails to follow group behavior. At this point, any of the special topics previously mentioned could be covered if appropriate, i.e., a discussion of antacids under sodium bicarbonate. Those items of special interest to the pharmacist would be reviewed, i.e., pharmaceutical uses, incompatibility behavior, cautions to be observed in usage, storage problems, if present, poisons and antidotes. Care must be taken in covering each item to tie it in with the specific property or properties of the compound involved if maximum teaching effectiveness is to be achieved. Finally, analytical procedures would be discussed if a special facet of importance is present.

The special topics suggested for coverage at some appropriate time during the course are: antacid behavior, saline laxative behavior, complexation-chelation-sequestration, action of ions on proteins, and essential minerals.

While an effort should be made to emphasize important compounds, this can be overdone. Even though one substance may be used more frequently than another, at the time of actual usage, the frequency of use does not alter the need for an adequate knowledge of its properties in either case. When necessary from the time element, we have made use of the New Jersey Prescription Survey by Dr. Voigt of our Pharmaceutical Extension Service as a guide in this matter to some extent.

In our course, we have tried two teaching techniques which proved valuable. "Study Sheets" have been compiled for the students. Neither of the textbooks give a good series of drill questions for student guidance and home work. The Study Sheets, one for each of the topics listed in the course outline, include definitions of terms, properties and uses of compounds, identifications, and sample prescriptions with or without incompatibilities. Provision is made throughout each series for equation writing drill. Emphasis is placed as much as possible on thought and reasoning.

We have also used displays of official compounds and preparations together with proprietary trade packages to tie in with our teaching. To develop student interest they were required to study the ingredients present in each and discuss their purpose, and their role in the ultimate use of the preparation.

An Integrated Approach to Inorganic Pharmaceutical Chemistry

At Rutgers, we have discussed the role of Inorganic Pharmaceutical Chemistry in the five-year curriculum for some time. At present, we are considering the possibility of an integrated approach to Qualitative Analysis, Quantitative Analysis, and Inorganic Pharmaceutical Chemistry for the second professional year (twelve credits taken over two semesters). There are several reasons for considering such an integrated one-year course. By including the analytical courses in the Inorganic Pharmaceutical Chemistry course, we would hope to tie the work more closely to our students' major field--pharmacy--without sacrificing his general chemical background. There is a similarity of subject matter and theory throughout these three courses, the difference being largely in application.

We would hope to have more thorough coverage by elimination of much of the duplication which exists in these subjects. Thus, for the average and poorer students, we could make a concerted effort at mastering a given concept at one time instead of treating it for a time in one course and then dropping it and coming back to it in a later course. Usually by this time, the average student has forgotten too much, so that in effect it is necessary to start over again. On the other hand, by this kind of unified treatment, one would not have to bore the good student by this, to him, unnecessary repitition. The course could be so set up that this better student would be given a break and progress to more advanced phases of a given topic, a thing very difficult under the present system. In turn, by elimination, or at least cutting down the time spent in unnecessary duplication, more thorough coverage of other areas should be possible.

The organization of such a course would be such that the coverage of the usual theories and methods of the analytical courses would not be changed, rather the classical order of presentation would be changed, as would the actual substances used for the laboratory aspects of the course.

The organization would be built around the Inorganic Pharmaceutical Chemistry course. Qualitative Analysis, within limits, fits faily well into periodic classification. The alkali metals make up Group V of the qualitative scheme, the alkaline earths Group IV, Group II consists of the typical elements and some members of the IB and IIB families of the periodic table, and finally, Group III is made up of the transition elements, except for the two classical amphoteric metals. Similarly, the acid groups of qualitative work well into the periodic classification, i.e., the halogens make up the major part of the silver precipitated group of anions. Since the pseudohalogens are usually included in the discussion of the halides, this presents no problem.

Quantitative Analysis would be worked into the course whenever a good illustrative situation was being discussed. For instance, volumetric procedures could be introduced at the time calcium salts are being studied. Calcium bromide could be determined by oxalate precipitation and permanganate titration, the official method. Certainly, this is a better illustration of the permanganate titration for the pharmacy major than the classical determination of an iron ore. Similarly, iodometric precedures can be introduced with Ferric Chloride Solution N.F. An excellent gravimetric procedure would be the official procedure for alum.

For the laboratory work, official methods of analysis would be used. In the case of qualitative work, it obviously would be necessary to include a study of scheme to give the student an overall picture of the separation techniques necessary before the identification tests, official whenever possible, can be applied.

Samples serving as unknowns would be official compounds, official preparations, possibly some common proprietaries, insecticides, simple cosmetics, etc. Solids would be issued as such, rather than in solution in order to give the student the needed practice in preparation of his own solutions. As the student progressed, he could be given more difficult preparations as unknowns.

Initial qualitative laboratory work would involve identification of the cation and anion only. However, as the work proceeds, he would be expected to take an official substance, identify it, run the trace element tests, and determine quantitatively whether or not it meets the quantitative standards set for that substance.

Some teaching problems certainly would arise, and it has been pointed out that some students might have difficulty in transferring credit to other fields. However, it is our feeling that an integrated course of this kind has more than enough advantages to counterbalance the objections.

SYLLABI OF INORGANIC PHARMACEUTICAL CHEMISTRY COURSES.

PHARMACEUTICAL CHEMIST'S APPROACH.

Taito O. Soine

I must confess that I am a little confused with respect to the title for this presentation which, to me, amounts to "The Pharmaceutical Chemist's Approach to Teaching Inorganic Pharmaceutical Chemistry". It has always been my impression that we are trying to carry out a given job of teaching and that there should be a certain amount of uniformity to the presentation. It would seem almost to be fostering class distinctions within our own ranks to admit that a particular subject matter could or should be interpreted in a substantially different way by inorganic chemists and pharmaceutical chemists. Admittedly, we may have diverse backgrounds but it would seem that, at the elementary level where we are teaching (i.e., freshman), the backgrounds of both species of instructor would pretty much coincide. The principal difference, as I see it, is that a teacher trained solely in chemistry with no background in the biological sciences (e.g., physiology, zoology, pharmacology, bacteriology, etc.) would have to indulge in a certain amount of self study in these disciplines in order to backgroung himself to the extent that the pharmaceutical chemist, presumably a pharmacist, already has by virtue of his required training. This kind of adaptation has been carried out successfully, however, by many chemists who are today skillfully teaching our pharmacy students. Thus, I cannot make the assumption that Dr. Discher and I differ radically in our presentation of subject material although I may possibly have a tendency to emphasize the biological aspects more heavily. If we do differ, I hope that he does not have the feeling about me that the late Dean Rufus Lyman once said (1) existed between general chemists and pharmaceutical chemists -- "To the general chemist pharmaceutical chemistry is what the side-winder is to the rest of the crotalus family".

The first question one might ask oneself with respect to the syllabus in Inorganic Pharmaceutical Chemistry is whether there is need for such a course or not. In my opinion there is such a field of study and, I believe, it represents a somewhat important segment of medicinal agents. The fact that organic drugs have been invading the medicinal field at an increasingly greater rate is sometimes taken as an indication of a diminishing usefulness of inorganic drugs. Nothing could be further from the truth. I say this with conviction and in all seriousness although, by virtue of training and research interest, I would classify myself as primarily an organic pharmaceutical chemist. However, as a co-author of one of the inorganic pharmaceutical chemistry texts, I have found it necessary to satisfy myself that this is a worthy field of study. A documentation of the importance of inorganic chemicals in pharmacy and medicine was published in the Journal of the American Pharmaceutical Association (2) in 1955 wherein the trends in N.F. basic drugs are graphed over the period 1916-1955. Aside from the fact that the noticeable trend in official recognition of botanicals is steadily downward and in organic medicinals is steadily upward, one is struck by the fact that a steady 12 to 15% of inorganic drugs have persisted over the years to provide a very flat curve in the graph. This may be taken as an indication

that we have a hard core of useful inorganic medicinal agents which will probably not change substantially within the forseeable future. It is true, of course, that some may be deleted but research apparently turns up enough useful new inorganic compounds to supplant the deletions and maintain the percentage of official occurrence. The picture is virtually the same in the U.S.P. which currently contains approximately 15% inorganic drugs. The above figures do not include those metallo-organic drugs which are used primarily because of the organic moiety nor does it include those metallo-organics which are used because of the inorganic component (e.g., arsphenamine, stibophen, etc.) but which are traditionally considered with organic medicinal agents.

If my argument is sound with respect to the continued existence of this steady 12 to 15% of inorganic medicinal agents the second question we must ask ourselves is how to best implement the teaching of the subject material. This question immediately brings us into the area of considering the prerequisites to the course as well as to a consideration of the course content itself. It is my understanding that, at times, the proposal has been advanced that general chemistry be combined with inorganic pharmaceutical chemistry in the standard one year course. This would also include qualitative analysis as a portion of the course work. I am at a loss to understand how it can be done without sacrificing one or the other or, probably worse, sacrificing both.

Let us look at the course in general chemistry for a moment and consider whether we have a clear picture of what is being offered in this area. The Pharmaceutical Curriculum (3) emphasizes the need for a very substantial course in this respect and further makes the observation that such a course should have a judicious balance of descriptive and theoretical chemistry. The descriptive material is pointed out as being particularly pertinent to the study of pharmacy. I have no quarrel with this statement but I do have a strong feeling that it will be difficult of attainment in light of the present day teaching of general and inorganic chemistry. Indeed, the situation with respect to the teaching of inorganic chemistry, which is essentially descriptive in nature, had reached such a state about 10 years ago that the 116th meeting of the American Chemical Society found it desirable to conduct a "Symposium on the Place of Inorganic Chemistry in the Undergraduate Curriculum". The symposium papers (4) were replete with such statements as:-

> "a large majority of schools have to all practical purposes ceased offering instruction in inorganic chemistry"
>
> "schools are graduating "professional chemists" who do not know the properties or reactions of simple common chemicals, who cannot suggest means of preparing or purifying simple inorganic substances, and who do not recognize the hazards involved in certain reactions of common inorganic reagents"
>
> "the content of the field of general chemistry has expanded to the point where one cannot cover the material adequately. In the process of elimination of material to be covered, it seems almost inevitable that the principles must be retained. The net result is that more and more descriptive material is being left out of the course"

"We must realize that the first-year chemistry as taught everywhere is general chemistry and not inorganic"

These statements merely illustrate the general trend that has been in process for many years and I believe it to be a good and reasonable trend because chemistry has been becoming more and more of a science over the years. Of necessity, the early years of chemistry saw a predominance of empirical descriptive chemistry which gradually yielded to the developing theoretical aspects of chemistry. And yet, one must recognize that the theoretical aspects were a direct result of the descriptive considerations and that the worthwhileness of a theoretical treatment is determined, even now, by its ability to explain adequately the purely descriptive phenomena. Certainly, if a choice had to be made between the theoretical and descriptive areas of chemistry in the general chemistry course one would have to select the theoretical area as the most desirable without in any way minimizing the value of the descriptive area. I feel that there has been a certain amount of confusion on the part of many pharmaceutical educators in considering the general chemistry course and its content. To illustrate this point let me cite an example from my own experience. Not too many years ago we had a visit from one of our eminent educator friends during which he commiserated with us on not having developed a "physical pharmacy" course. At the same time he promised to send us an outline of his purportedly "model" course which he felt was just what was needed. In due time we received the outline and carefully studied it in order to orient ourselves into the field. It was soon noticed that there was a marked resemblance in a large part of the course outline to that of the general chemistry course that was being taught to our freshmen. Upon submitting the course outline to our chemistry department we were informed that, in great measure, this was already being taught to our students and, in fact, had been a part of the course for years. It was most flattering to find that we were offering a double-barreled course, namely general chemistry and physical pharmacy all wrapped up in one bundle. In a way, it lent substance to a suspicion I had held for some time with respect to physical pharmacy and the ideas that many people had about its specific area of teaching. This suspicion stemmed from an experience we had with another eminent educator who, when bluntly asked for a description of a physical pharmacy course, somewhat naively assured us that "although we cannot at present define exactly what we mean by physical pharmacy, we think the course should be instituted by name at least and we will later worry about filling in the course content." Notwithstanding the confusion concerning physical pharmacy at that time I believe there now has been created a course content in most schools that can properly be termed physical pharmacy. I do not intend to enter further into the pros and cons of physical pharmacy or into the similarities and differences between physical pharmacy and general chemistry. I am sure that there is a proper division of labor between the two areas and it is a certainty that the general chemistry course is for the most part theoretical in its approach to the subject material.

Thus far we have treated mostly on the general chemistry aspect of the one year elementary chemistry course required of our students. It should be emphasized that qualitative analysis is an integral part of this course work. Qualitative analysis, as you know, has to do primarily with a somewhat comprehensive treatment of ionic equilibria in chemical reactions. If there is any part of general chemistry that lends

itself to being described as offering some descriptive study, it would be qualitative analysis. The systematic analysis of cations and, in some cases, anions helps to establish some sort of contact with actual chemical identities. One could effectively argue, however, that much of the student's effort in qualitative analysis is wasted by the cookbook approach to the laboratory work wherein they become rather effective technicians but often are at a loss to explain the successful outcome of their experimentation. In assessing the coverage of ions in qualitative analysis one finds that the coverage of cations is excellent although there are a few that are not covered in the standard systems of analysis. The same cannot usually be said of anion analysis with particular emphasis on the anions that are of importance to pharmacy. This may be ascribed to lack of time which, however, does not remedy the situation. In many cases the qualitative analysis course consists only of cation analysis without any particular emphasis on anion analysis except that which is incidental to the consideration of cations. Inasmuch as some of the important cations are associated with organic anions it is small wonder that students in inorganic pharmaceutical chemistry courses look with misgivings upon the mention of these salts. There is a silver lining to this cloud, however, in the fact that modern general chemistry courses quite frequently include a brief survey of the major organic classifications so that students are at least conversant with the nomenclature.

In considering the background of students coming into inorganic pharmaceutical chemistry in a realistic way one must recognize the shortcomings as well as the strong points of their training. One cannot accept the training at what seems to be its face value and carry on with the assumption, "You have had this in previous courses so we will not consider it." It is necessary to determine, by consultation with chemistry instructors or perusal of student notes, just exactly what has been covered in the prerequisite course. I am of the opinion that the introductory course in general chemistry frequently is merely an introduction to the nomenclature and theory of chemistry which needs review and nourishment to bring it to full understanding by the student. Orr expressed somewhat of the same opinion at the last Pharmaceutical Chemistry Teacher's Seminar (5) when he emphasized the importance of reviewing fundamentals. It is of some interest to note his statement that many of his students have "wondered why these things were not pointed out to them in a way they could understand before?" I have much respect for Dr. Orr's teaching abilities but I submit that, if he had been the general chemistry teacher and the students had later taken a review in fundamentals from a chemistry teacher, the picture would have been exactly reversed. We have had the same experience at Minnesota and, knowing the qualifications of the chemistry teachers, I do not flatter myself that I am necessarily a superior teacher when these same comments come my way. Rather, I have a strong feeling that the students have been "conditioned" by previous exposure and, by virtue of a slightly different approach, correlate previous learning with the review material and thereby exhibit a much greater comprehension. My preceding statements should not be interpreted as condemning either the general chemistry teacher or the inorganic pharmaceutical chemistry teacher, but rather should convey the impression that review by the latter is a desirable approach in reinforcing the learning process.

The picture that I have painted of general chemistry and qualitative chemistry has a definitely positive contribution with respect to the pharmacy student. Whereas the chemistry student is definitely handicapped by the lack of descriptive material offered in his general chemistry course, the pharmacy student is in the position where he is well prepared with theory and is just launching into the descriptive phase of general chemistry in the area where he is most vitally interested, namely inorganic pharmaceutical chemistry. Blauch and Webster (6) have emphasized that the course "should be designed to amplify and complement the descriptive information of general chemistry, qualitative analysis, and quantitative analysis". They further point out that "It is a beginning in the process of building up a pool of information which the pharmacist must have at his disposal". Thus, the essentially descriptive aspects of inorganic pharmaceutical chemistry are pretty much a matter of record backed up by the opinion of most people in the field. This in no way minimizes the importance of the course content despite the feelings of those high minded individuals who feel that any departure from theoretical aspects is a desertion of principle. On the other hand, although descriptive treatment preempts the major emphasis in inorganic pharmaceutical chemistry one should not lose sight of the valuable opportunity presented to offer a more sophisticated discussion of basic theoretical principles. Of special interest in this connection would be more extended considerations of acidity, basicity and other ionic phenomena as well as considerations of Periodic Table relationships with respect to physical properties. I do not feel that this course should be a "second year" college chemistry but the extended treatments of selected topics of interest to pharmacists should approximate that level of study without losing sight of the idea that the emphasis of the course is primarily descriptive.

Granting that there is some truth to what has been said up to this point I must return to the basic premise of my talk, i.e., "How does the pharmaceutical chemist's approach differ from that of the inorganic chemist?". My introductory remarks have, I hope, made it clear that I do not feel there is any real difference provided the inorganic chemist schools himself to an adequate degree in the biological background necessary to teach a subject with pharmaceutical and medicinal implications. How then does one approach the teaching of such a course? If we leave out the purely chemical and theoretical considerations which presumably are part and parcel of any effective teaching of the subject material I am left with certain definite ideas that I believe to be valuable. Inorganic pharmaceutical chemistry is often considered to be a dry and uninteresting requirement to be met and conquered by the student. To this end, one can emphasize certain aspects of inorganic chemicals in order to capture the student interest. Undoubtedly, the pharmacy student has entered into the program of study because he or she has an interest in things medical. This, then, can be utilized as the catalyzing influence in furthering the study of inorganic pharmaceuticals. The crux of the matter certainly lies in the answer to the question, "In what way or ways does the inorganic pharmaceutical chemical and its chemistry differ uniquely from the same chemical considered in an industrial context". Some of the points that might be emphasized to implement this differentiation are suggested in the following statements.

Historical aspects of medicinal agents are often very interesting and provide a human interest motive for retaining knowledge about the drug. The story of calomel as a salivating agent, its overuse and abuse, and the subsequent rise of homeopathy is certainly worth telling. The history of usage of gold salts over the years from the time that kings used them as a "royal physic" to their present day application in lupus and arthritis is extremely interesting. Dr. Buchanan, Junior Surgeon of the Glasgow Infirmary, introduced hydriodic acid into medicine with the comment, "It appeared to me, however, that it would be well to save the stomach the labor of preparing hydriodic acid, by giving, for the purposes of medicine, not free iodine, but the hydriodic acid itself." This introduction to hydriodic acid serves to provide distinction to an otherwise simple hydrohalide acid. Naturally, a treatment of inorganic medicinals in this manner requires a knowledge of pharmaceutical and medical history as well as a nodding acquaintance with current research and modern medicinal agents.

Interwoven with the historical consideration of inorganic medicinal agents is the important matter of the rationale behind the introduction of drugs into therapy. It is certainly reasonable to believe that all drugs introduced into therapy must have had some kind of reason for coming into being. The reason may now appear to be hare-brained and irrational or it may be eminently correct but in either case it serves its purpose as a teaching tool. As an example of what is meant here consider the introduction of gold salts into the therapy of rheumatoid arthritis. Following Koch's demonstration of the activity of gold cyanide vs the tubercle bacillus in 1890 the gold salts were favorite ammunition for any and all disorders that were thought to be tubercular in nature, including tuberculosis itself. Rheumatoid arthritis, a supposedly atypical tuberculosis, was thus the object of gold therapy and even today is considered to have some merit although it is certain today that the disease is not tubercular. Strontium salts were once introduced into therapy because it was thought that there was a slower release of the anion from strontium than from other common cations with a subsequently more prolonged action. Lithium salts were introduced to therapy on the basis of the observed water solubility of lithium urate as contrasted to sodium urate. This factor was expected to solubilize the known deposits of uric acid in gouty conditions ignoring the fact that, in the presence of large supplies of sodium, potassium and ammonium ions, it is no more possible for soluble lithium urate to form than it is for soluble sodium oxalate to form in the presence of calcium ions. More precisely aimed therapeutic bullets are represented by the introduction of Medicinal Zinc Peroxide for the treatment of wounds suspected of harboring anaerobic or microaerophilic microorganisms as well as the many useful antacids such as Magnesium Trisilicate, Aluminum Hydroxide, etc. It would be well for the instructor to know, if possible, the rationale behind each and every chemical in this classification.

Unique problems with respect to the dispensing, preparation, use, and preservation of inorganic medicinal agents also serve to lend distinction to drugs from a pharmaceutical viewpoint. It is indeed a callous student who does not gain new respect for the toxicity of mercury bichloride when shown the precautions taken to prevent accidentical poisoning such as tablets of distinctive shape and color as well as distinctive shape and color as well as distinctive shaped bottles. Where can it be better to

tell the student about the dangers of zinc stearate which, because of its extremely fluffy nature, requires a spring top can to prevent innocent babies from spraying the crib with a powder that has been known to cause pneumonia? With respect to zinc stearate, I have my students rub some between the palms of their hands and then have them run water over the waterproofed skin area. This neatly illustrates the use of zinc stearate as a waterproofing agent for strategic areas on small babies. The sterilization of sodium bicarbonate solutions also presents a neat problem that ordinarily would be of little interest to an industrial chemist. A favorite of mine is the therapeutic incompatibility between sodium salicylate and sodium bicarbonate, commonly prescribed together, wherein the sodium bicarbonate lowers the renal threshold for salicylate excretion markedly and consequently lowers the plasma salicylate level sharply. Another interesting case along these lines is with respect to the toxicity of boric acid, often thought to be a rather innocuous antiseptic. At the beginning of World War II, boric acid ointment was considered to be a safe and effective treatment for burns until it was used on extensive burn areas and found to be absorbed in sufficient quantities to cause typical boric acid poisoning. Further emphasis of the toxic effects of boric acid may be gained by citing the case in a large eastern hospital where boric acid was mistakenly used in place of dextrose in infant formulas with the subsequent death of several babies. Any number of other illustrations could be used to amplify this point but these will perhaps suffice.

The fourth general category which I feel to be somewhat unique is the aspect of elementary pharmacology in relationship to inorganic pharmaceutical chemicals. Certainly, a brief delineating statement as to the position occupied by a particular drug in the scheme of medicinal agents is not without value, and by this I do not mean that it can be disposed of by simply stating that it is an antacid, antiseptic, antiluetic, etc, I am aware that there has been no small amount of criticism offered concerning the use of some of the elementary concepts of pharmacology in the teaching of pharmaceutical chemistry. Strangely enough, the criticism is directed almost entirely toward the problem with respect to inorganic pharmaceuticals whereas in many cases the criticism is lacking when the teaching of organic pharmaceuticals is considered. I will stand in bare-faced admission that I utilize a certain amount of elementary pharmacology as well as physiology in my teaching. I am also acutely aware of the fact that this pharmacology is quite often not given elsewhere because of the press of time and the greater amount of time devoted to the more numerous and glamorous organic medicinals. In many cases, I am convinced, my coverage is the only one they encounter in their training. This imposes a responsibility on the inorganic pharmaceutical chemistry teacher to be accurate in his facts and explanations and to coordinate them with the thinking of the regular pharmacology staff. Personally, I feel it desirable to check all of my statements with our own pharmacologist as well as with the pharmacology staff of the medical school. I am not entirely sure that there is as much objection to the use of a limited amount of pharmacology as has been indicated by some. Virtually every review of inorganic chemistry textbooks, where a brief pharmacological treatment is employed, is favorable and in some cases laudatory. Just how far one goes in the pharmacological (and physiological) treatment is a matter of judgement for the individual instructor. In my own case I attempt to limit the discussion to the point where I feel that a reasonable basis has been

established to explain the therapeutic use of a particular drug. It is possible that a pharmacologist would dispute the fact that the limited treatment given to any particular subject should be graced by the name of pharmacology. However, one is dealing with freshmen and it is imperative that the background deficiencies of these students be recognized and proper allowance made. For examples, simplified diagrammatic explanations of organs and their function are necessary to orient the student properly but it certainly would not be desirable to go into elaborate details of tissue differences, percentages of normal constituents, distribution percentages of drugs in organs and tissues, etc. Most students seem to grasp the function of the nephron unit and its relationship to the kidney as a whole as long as it is presented diagrammatically although they might not recognize either the unit or the kidney if confronted with them. Having once presented the kidney and its function, it is relatively easy to show how glomerular filtration and tubular reabsorption operate with respect to some of the inorganic chemicals. With this physiological background it is possible to discuss in a more meaningful way the mode of action of osmotic and mercurial diuretics as well as the mechanism of kidney stone formation and its prevention by the use of aluminum hydroxide or subcarbonate. The student also learns the gross facts about formation of urine which he can later study in physiology with greater comprehension. Getting away from the kidney, one can cite the time-honored description of osmotic cathartics. It is not difficult to convey the idea of the osmotic cathartic but surely the student is left with a question mark in his mind if the discussion of cathartics ends at this point. Therefore, it would seem to be only good teaching to at least briefly outline the other categories of cathartics with examples. A discussion of antacids is nicely accompanied by a brief outline of the manner which systemic antacids operate vs non-systemic antacids. An adequate and easily grasped schematic diagram is that adopted by Goodman and Gilman (7) or that proposed by Green (8). The function of oxygen in oxygen tents and masks is without much value unless the student has an elementary concept of the relationship of the lungs to the circulatory system. A simple diagram takes most of the mystery out of the use of this gas. In addition, it provides the basis for the later consideration of Soda Lime as a carbon dioxide absorbent in closed systems. An elementary presentation of the course of events involved in iron metabolism is also a useful preface to the discussion of iron compounds with respect to anemias. Much of the precise knowledge has been developed within the past 10 years due to the use of radioactive iron. One does not need to go into great detail in this connection but what you can give serves to background the students to the extent that the differences in common iron salts become significant. In addition, a brief classification of anemias is a necessity in further orienting the student with respect to intelligent use of iron salts.

These, then, are some of the points wherein I feel that the pharmaceutical chemist's emphasis in teaching a course in inorganic pharmaceutical chemistry might differ from that of the strictly inorganic chemist. Personally, I find much satisfaction in presenting the course in this manner and unsolicited comments from former students lead me to believe that they, too, derive benefit and interest from it.

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EVALUATION OF STUDENT ACHIEVEMENT

Cyril J. Hoyt

I have taken the liberty of slightly modifying the title by using the term achievement rather than performance. Achievement is used to include performance as well as understanding and feelings such as attitudes, beliefs and mental sets. The term behavior is somewhat more inclusive than achievement though in this discussion the behaviors considered are achievements. This broad meaning of behavior which includes feeling and thinking as well as overt action is in line with the psychologist's use of the term.

In this paper I plan to give attention to two main points: (a) the purposes of evaluating student achievement and (b) the how or the means of evaluating student achievement. The discussion of this latter topic will give attention to the four technical problems faced by an instructor who wishes to systematize his evaluations of student achievement.

It will help to clarify our communication if we make explicit, at the outset, the variety of means of evaluation. When we speak here of evaluation we certainly do not wish to limit our thinking to examinations and certainly not to recognition type items. If the classes are not too large some informal evaluation is done by oral questioning of individual students in class or in laboratory periods. Evaluations of laboratory work may be done by direct observation of students at work and/or by rating written reports of experiments performed in the laboratory. Hence, references to evaluation here will include this wide variety of devices for collecting information about the numerous behaviors of students which instructors seek to influence by instruction and by the use of student assignments.

As one further preliminary I would like to quote from Tyler's[1] discussion of the relation of evaluation to curriculum and to instruction. This view is one to which I subscribe and to which many if not all of you also subscribe. The four basic tasks in developing a curriculum or a plan of instruction are:

1. To determine the objectives which the course or program should seek to attain.

2. To select learning experiences which will help to bring about the attainment of these objectives.

3. To organize these learning experiences so as to provide continuity and sequence for the student and to help him integrate what might otherwise appear as isolated experiences.

4. To determine the extent to which the objectives are being attained.

One purpose of evaluating student <u>achievement</u> is to check on the <u>effectiveness of instructional practices</u> and on the effectiveness of particular <u>student assignments</u>.

[1] T. Tyler, Ralph W. "Achievement testing and curriculum construction." In E. G. Williamson (Ed.) Trends in Student Personnel Work. Minneapolis: University of Minn. Press, 1949.

For example, an instructor may be concerned about the usefulness of one set of laboratory experiments rather than an abbreviated set or about the relative gain in understanding certain principles achieved by students as a result of more thorough and extensive student reports on laboratory experiments. One may ask, does every experiment performed in the laboratory warrant a uniform emphasis in student reporting or are some experiments of such major importance that more data should be collected and perhaps more time devoted to writing the report? These are questions that begin to relate student achievement to such student assignments as readings, written reports, experiments performed, lectures attended, work experiences, or other kinds of student activities which one hopes will help students gain certain understandings and develop the ability to apply principles.

When the instructor considers the effectiveness of student assignments for helping students understand and apply principles of some particular subject matter field he is then engaging in one of the most important roles of his profession as a college instructor. He is selecting, modifying, inventing or writing course content which has both eyes on students and their learning processes and both eyes on a comprehensive view of the important subject-matter field in which the instructor is currently a research scholar in only one or a few particular specializations. This process of devising or choosing student assignments involves more than a selection of the particular portion of the subject-matter of pharmaceutical chemistry you plan "to cover" in the particular semester. In addition, the instructor considers what knowledges, skills, habits, understandings and attitudes he hopes his students will develop during the particular course or semester.

Since many complex understandings, habits and skills are not easy for students to achieve, instructors must devise assignments that will help students learn the components parts of complex understandings and then devise other assignments that will aid them in seeing-how and in practicing putting the parts together - that is, in synthesizing and thus reorganize the newly learned principles with principles that they previously knew from <u>earlier</u> instruction (either in your course or in some preceding ones). In some cases certain understandings may be so important that you want students to apply principles learned in rather divergent areas. If so, assignments should be devised to give students some practice in applying principles. Such assignments frequently take the form of problems to be solved in the laboratory or as out-of-class papers.

Most textbooks of today have not given sufficient attention to the learning process to be a safe guide to use without supplementation and selection. The instructor who is evaluating student progress frequently is aware of the understandings that are incomplete, erroneous or otherwise inadequate in the large proportion of his class. When such inadequacies are noted supplementary instruction and/or additional student assignments can be made prior to the next place in the course that students will be expected to apply these principles or to build further upon these understandings. If conditions such as time or other pressures do not permit the instructor to remedy the inadequacies discovered by such an evaluation, at least, the instructor will often be able to make some adjustments for subsequent classes.

A second purpose of evaluating student achievement is to provide information about the status of individual students. This kind of information is sometimes given back to students, to prospective employers, to parents or others in the form of grades or some general quality achievement-level-rating such as grade point average or honor point ratio.

Likewise, when earnest students become aware of the bases upon which their written work, examinations or laboratory techniques are evaluated they are given operational definitions of the behaviors the instructor considers important for the course. Hence, the later study efforts of these students and of those in subsequent classes are directed toward learning what seems necessary for earning a high score on the examinations, papers prepared and other performance ratings used for evaluating any of their achievements. Recognition of such effects on students helps us to see the motivational effects of evaluation. This also points to the importance of informing students about the various bases we use for judging the quality of their achievement as well as to inform them regarding their ratings. Some instructors are reluctant to inform certain below-average, average or slightly above-average students about their grades because the instructors assume that fear-of-failing is the most effective motivational device available. Actually psychological studies do not indicate that fear-of-failure is a very effective type of motivation. In college classes, there are usually relatively few students whose grades are so close to the borderline that threat of failure is a real motivation. Most students are likely to look at the constant threat of failure in their courses much the same as most of us look at the danger of tornadoes or of a lightning bolt. The danger is there but the probability of occurrance is too low to cause much concern. Rivalry, competition, the desire to improve, real interest in the subject-matter, personal commendation from the instructor and special privileges earned are examples of far more effective motivational devices than fear-of-failure. All of these devices can be used by the college instructor who evaluates the different aspects of student achievement as the semester is progressing.

The above considerations have dealt chiefly with the so-called "energizing aspect of motivation - that is, the increase in the general level of students' study activity." When students know their work is evaluated, feel the evaluation is fair and specific and promptly learn the results of the evaluation the general level of student activity is increased. It is important that the instructor make his evaluations of such a nature that students be stimulated to study-activities that are beneficial to them. Hence evaluation of student achievement also has a selective influence on the study-activities of students. Instructors should aim to devise their evaluations in a manner that will reward most highly the students whose study activities are the best. For example, when true-false, multiple-choice or other examination questions are couched in the direct language of the textbook or that of the lecturer, high scores are often rewarded to those who have memorized textbooks or the lecturer's wording or style and thus encourage attention to specific wording rather than to meaning. There may be times when this is desirable but students' understanding of vocabulary may often be adequately tested by other means, such as asking them to criticize certain definitions of terms some of which are faulty in certain fundamental details. The point of this example is to show that the

kind of evaluation used has a "selective" influence on students' study-activity. On this point it should be mentioned that the selective effect of the same type of examination question can change over a period of time. A certain instructor in psychology used a matching test consisting of a list of authors and a list of book titles to obtain a measure of the students' acquaintance with the literature in a field. This was an adequate test for its first use but on a second and subsequent use it stimulated students to memorize lists of authors and titles, a nearly useless type of study-activity. Another professor of a more technical course asked students to write definitions of terms discussed in the first quarter's work. So much emphasis was placed on this type of question on the final examination that students in subsequent classes developed lists of definitions which were memorized. Such study efforts may not be totally undesirable but they were inadequate for some students since they were credited with understanding when they had memorized rather poorly understood verbalizations.

A third purpose of evaluating student achievement is to provide instructors with a good basis for their own psychological security. Instructors need assurance of a job well done. Hence, evaluating student achievement gives the instructor evidence relative to the degree to which students are developing the desired behaviors.

In this connection it is appropriate to consider briefly two points which would be of concern to instructors who compare the scores of a class early in the semester with those for the same class near the end of the term. In such circumstances, does one expect his class members to differ among themselves more extensively early in the semester or late? If the examination is not too easy for the best students so they are permitted to show their superiority and if the student behaviors evaluated are those for which limits are high, most classes that have been instructed well will show more variability among its members after instruction than before. There are times, however, when the mastery of certain limited knowledges may be one of the chief goals of instruction. In such cases the superior students gain complete knowledge earlier than the less able students. If the evaluation does not give the superior ones an opportunity to show the additional development which occurred after they had learned the minimum essentials, the class will show only small variability among its members if the instruction has been effective in getting nearly complete mastery of the minimum essentials by all class members.

A second problem which may concern some instructors who evaluate the learning in a class by testing the same class early and again near the end of the semester is the small percentage increase in the mean schores. Suppose a class increases its mean score from 100 to 120 during a given semester. Is such an increase worthy of a semester's instruction or should an instructor be critical of such a small improvement? If one examines carefully such test results he is likely to find that many test items were answered correctly by nearly all members of the class early in the semester. On the surface this looks like a very small percentage of gain. However, if only fifty items were

known by all or nearly all class members before instruction and 50 is subtracted from each mean, the percentage of gain becomes 40%, one which appears somewhat more acceptable. Percentage of gain can be misleading if one does not study carefully the relation of the test content to that of the course and also the percentage of students answering each item correctly on the initial testing.

When examinations are given early in the semester or when the results of final examinations from the previous semester are available to an instructor in a sequence course, it is usually useful to examine the students' replies item by item so the instructor can learn which points were well understood initially by most class members and which points need reemphasis during the current semester.

Other purposes of evaluating student achievement such as placement and guidance of individual students will not be considered in detail here. Likewise we will not discuss the public relations purposes of evaluation or the uses of evaluation for testing hypotheses relative to establishing a body of knowledge on which educational practices can be based. We have considered, however, the three most pertinent purposes of evaluating student achievement, (a) testing the effectiveness of instructional practices and student assignments, (b) providing information about the achievement of individual students and motivating students, and (c) providing instructors with a good basis for their own psychological security.

Four Technical Problems Involved in Evaluating Student Achievement

Hand-in-hand with the selection of the general course content area must go a consideration of the instructional goals. In general terms the goals find their main bases in the work of the men in profession with due consideration given to best practice and desirable future development in the profession. With this in mind, the first technical problem in evaluation is the determination of the objectives of instruction and the description of these objectives in terms of desirable behaviors on the part of those who have completed the course satisfactorily. The instructional or course objectives thus stated are in terms such as, what knowledges, what skills, what habits, what attitudes, what specific reasoning or problem solving abilities, what abilities to use sources of data and in what areas and levels of difficulty are applications of principles expected. The second technical problem involves considering the variety of situations in which adequately prepared former students exhibit these specified behaviors. The third problem requires the adaptation of these situations or newly devised simulated situations in which current students themselves (or observers, if necessary) can make a record of the students' behavior in these situations. The fourth problem is concerned with devising means by which the records of individual students can be evaluated in terms of the behaviors specified as course objectives. These are not easy tasks but fortunately they are all closely related to the main job of classroom teaching. When one selects content he considers

which knowledges, principles and special ways of reasoning are most important for the students to achieve. Also, the attention instructors give to student assignments and to specifying laboratory work are directed toward helping students learn facts, skills, reasoning methods and abilities needed for applying these. It seems, however, that when instructors keep in mind the four technical problems of evaluation that are outlined above, they do find that their students become more sensitive regarding improved ways of applying their study efforts and also become more highly interested in their own development because their goals for each particular course become clarified in their minds. They have specific milestones along their five-year road to professional competence. Specific information on evaluations along the way are useful in helping them to remedy their errors, in redirecting their efforts and, perhaps, even directing efforts toward specialization. Such information for students becomes more useful to them as it becomes more frequent and more specific in terms of skills, habits, knowledges and reasoning abilities. Instructors' suggestions to individual students for redirecting their efforts are particularly helpful if given in the light of evaluations of specific abilities.

In the interest of considering these four technical problems of student evaluation in more detail, it will be useful to consider five classes of instructional objectives that seem of most direct concern in chemistry courses in a professional college. In any particular course emphasis may be placed on certain of these following classes of objectives while others may be totally ignored. The selection of objectives is often decided by the individual instructor though in some instances the whole college or departmental faculty may suggest guide lines for him to follow. The following are classes of instructional objectives which are worthy of consideration in professional college courses.

1. Acquisition of information - This includes knowledge of specific facts, terminology and principles. It is desirable for students to have a sufficiently thorough grasp of much of this knowledge so that they are able to use it in solving problems and in applying principles to situations new to them. Their knowledge should be sufficiently thorough to enable them to distinguish misconceptions and superstitions from scientific fact.

2. Abilities required in using scientific methods of experimental research with the use of induction, deduction, probability and associated generalizations. In an elementary college course in zoology, the instructors specified three types of student behavior as components of the scientific method. That portion of instruction and evaluation concerned with this objective were directed toward the three abilities: (a) the ability to formulate reasonable generalizations from specific experimental data that were recorded carefully and presented to the students; (b) the ability to plan experiments for testing hypotheses that were clearly formulated for the students; and (c) the ability to apply principles to new situations. In some advanced science courses it is suitable to include in scientific method the use of these abilities in more complex situations and the development of other abilities such as the selection of pertinent data from a mass containing much that is irrelevant and the formulation of testable hypotheses which are pertinent to the solution of a complex research problem.

3. Class of objectives. Knowledges and skills required in locating information available in tabular and other source books used in the subject area and in the profession.

4. Study skills and laboratory skills that are characteristic of the particular subject. In certain chemistry courses this would involve work with chemical formulas and equations, in other course uses of specific types of laboratory apparatus and/or computational devices.

5. Ability to organize and write technical reports of research or other types of projects completed and/or the ability to read such reports critically. There are other less technical instructional objectives which, though important, do not seem to be as obviously achieved through direct instruction but acquired through instructors' subtle encouragement and aid in providing satisfaction for desirable student interests and attitudes.

One approach to the formulation of detailed instructional objectives is to consider the contributions that each topic in a given subject-matter outline can make to the development of each of the types of student behaviors in the above list. Such consideration aids the instructor in planning student-assignments which will be useful for helping students develop the abilities stated as objectives for the particular course. If students discuss with the instructor difficulties they have in completing the assignments and the instructor informs them regarding their inadequacies and their achievements students will know how to redirect their efforts in order to achieve the desired goals. These suggestions are most appropriately given on the basis of more or less formal evaluation of students' achievement.

The instructor who selects and devises student assignments which are aimed at helping students develop the behaviors specified as objectives has already made progress on solving the second problem in evaluation, the selection of situations calling forth the behaviors specified. Often situations similar to those used for assignments can be used for examination items. Likewise, the instructor's rating of the quality of students' work on assignments serves as a basis for the evaluation of student achievement. When difficult test situations are desired these may often be devised by using applications from the early sections of subsequent courses.

Some student behaviors can be observed directly in the laboratory. However, the devising and using systematic observational procedures for each student is usually too time-consuming, though in some cases it is necessary especially in the use of certain delicate instruments and costly materials. Observational check lists are often found to be a useful means for determining a student's knowledge of a complex laboratory operation. Such procedures for checking students' precautions in the use of delicate instruments have been found necessary. The use of observational check lists to evaluate the work of each class member becomes very time consuming unless a plan for using self-report by students or laboratory assistants can be devised.

The third technical problem involved in evaluation is that of obtaining a record of student reactions to situations calling for the knowledges and other desired behaviors. This often taxes one's inginuity, especially when interests and attitudes

are in question. Fortunately, most achievement can be assessed by more concrete evidences than those in affective domain. Sometimes students make a product in the laboratory or test unknown substances for the presence of certain chemicals which the instructor knows are present or absent. These are effective means of determining how well students are able to perform certain laboratory procedures. The observational check lists provide another means of obtaining a record of student skills and procedures.

Other records of student reactions consist of verbal responses of various kinds. If the record is oral, the hearers must give evaluations based upon an immediate reaction. This variety of evaluation has been found to suffer many shortcomings such as wide sampling errors and low consistency. Oral examinations and oral responses of short answer type are still found useful, however, when the ratio of student number to instructor number is not too high.

Evaluation of the student behavior recorded in reports of experiments, reviews of research reports or other projects may require more than a single reading to give adequate attention to each of the behaviors exhibited in such a report. In evaluating reports of laboratory work it may often be desirable to rate separately such aspects as the quality of the data record, the adequacy of the description of procedures, the adequacy of the inferences drawn as well as the quality of the uses of English <u>and</u> computations. If one instructor wishes to include in his course grade a heavy or a small weight on any of these ratings, he should clarify his position to the students so they may apply their efforts accordingly. The practice of rating all these and other aspects of the report by a single number or letter is not as useful to the student as more detailed separate ratings for each objective.

When students respond to examination questions with replies of a paragraph type, such student records can be evaluated reliably and objectively if the reader will specify a definite plan for giving points and take time to rescore a small percentage of the papers to help maintain a consistency in his scoring procedure. It is most satisfactory to score in succession the replies from all students to a single question. If the reader must interrupt the scoring before all students' responses to one question are scored, it is desirable to rescore one or more papers at the subsequent sitting to re-establish the system devised for giving partial credit. These precautions of consistency in scoring are of less necessity as the scoring specifications become more nearly objective.

It is important that long answer responses be scored in terms of the behaviors to be evaluated. It is usually possible to score more than one behavior from written paragraph responses. Since the two or more behaviors may <u>not</u> be achieved equally well by any one student it is preferable to give each student a separate score on each behavior rated on each paragraph response. This makes for slightly more arithmetic on the part of the reader but does achieve greater specificity in scoring. It also enables the instructor to study the intercorrelations among the achievements of the different student behaviors.

DISCUSSION

The wisdom of separating students on the basis of ability into different laboratory or discussion sections was brought up. Such a sectioning of junior students, based on grades in science courses and mathematics and on ACE scores and high school evaluation scores, was reported to work quite well for laboratory instruction in the one instance in which it was tried.

Dr. Hoyt agreed that the use of the record of the student as a guide in subsequent instruction is good practice. "Usually you find that students can be stimulated a great deal by such separation. It is a good idea if it does not overload your instructional work too much. Obviously the most desirable would be to have an individual student where you know exactly how much he knows, what he knows, what he needs to know. . ." Working with him as an individual, as is true in working with graduate students, benefits the learning situation. Laboratory instruction provides opportunities for this. One can deal with individual students or groups according to their specific needs, and this is desirable.

Dr. Gisvold expressed some surprise that many of the teachers in colleges and universities perform as well as they do in view of their lack of training in education courses. Such training, if it could be obtained, may resolve problems arising in preparation of examination or in "many other ways of evaluating students."

Tuesday Session

Allen I. White

Chairman

[illegible]

The [illegible]

[illegible]

[illegible]

[illegible]

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SYLLABI OF ORGANIC MEDICINAL PRODUCTS COURSES

Edward E. Smissman

1) Basic Chemistry Aspects

The treatment of the basic chemistry concepts in an Organic Medicinal Products Course of necessity must be based on the chemistry courses which precede it in the curriculum. In different schools of pharmacy the position of the Organic Medicinal Products course varies from the sophomore year, in which medicinal products are given during the discussion of elementary organic chemistry, to the senior year where it is given after physical chemistry, biological chemistry and quantitative analysis. The length of such a course also varies; in some schools it occupies a complete year while in others it is given in one quarter of three to four lectures a week. The following table will demonstrate the non-conformity of the Big Ten schools with regard to this course.

School	Year	Periods	Total Credits
1. Illinois	4	1 quarter	4
2. Iowa	3	1 semester	3
3. Michigan	3 and 4	2 semesters	6
4. Minnesota	3	3 quarters	10
5. Ohio State	4	2 quarters	10
6. Purdue	3	1 quarter	3
7. Wisconsin	3	1 semester	4

Thus, it is evident, unlike elementary organic chemistry, which by tradition is given in the sophomore year and is usually a one year course, we have a ubiquitous course which makes it difficult to establish a rigid basic chemistry aspects syllabus. If we probe still further in establishing a syllabus we must also include the pros and cons of a laboratory to accompany the course. Of what merit would it be? Is it worth the expense? Should it be given, but only as an elective?

Still another thorn in the discussion of this compendium is the fact that in many schools physical chemistry is not given either before or after the Medicinal Products Course. Thus the presentation of basic concepts must be based on the physical principles obtained in the elementary general chemistry, qualitative analysis, and quantitative analysis courses. If the course is given in the senior year, obviously more time must be devoted to refreshing the student on previously discussed aspects as well as supplying him with a new, useful foundation.

The advantages of an Organic Medicinal Products Course based on sound fundamental concepts versus the course in which the principal emphasis is placed on memorization of structures and trade names is obvious. The latter makes for inferior preparation of the student as a future pharmacist, regardless of the field in which he may work. Two main advantages may be stated regarding a course

which has a strong emphasis on the aspects of basic chemistry; first, from the instructors standpoint it aids in the teaching of the pertinent material because it allows for broad generalizations concerning biological, chemical, and physical concepts of drugs. Secondly, it gives the student a firm foundation on which to build in the future as new material is added to his store of knowledge from the literature, institutes, and from extension service brochures. Because of the diversity of the position and the time alloted to this course in various curricula, the treatment I will offer is pointed toward a one semester, junior course having general inorganic chemistry, organic chemistry, and quantitative analysis as its prerequisites.

It is possible to divide the basic aspects into two arbitrary major divisions which have a common meeting place in the applied material of medicinal chemistry and pharmacy. These arbitrary divisions shall be assigned the headings "Organic Chemistry Basic Concepts" and "Physical Chemistry Basic Concepts." Biochemistry, for this purpose, shall be considered a branch of organic chemistry and quantitative analysis as an application of physical chemistry principles. Overlap of these two main headings can and should occur to a great extent. Topics to be included in lists of this nature are as follows:

BASIC CONCEPTS

Organic	Physical
Bonding	Solubility
Ionic bonds	Partition Coefficient
Covalent bonds	
Hydrogen bonding	Surface activity
Chelation	
Lewis theory	adsorption
Heterolytic bond cleavage	
Homolytic bond cleavage	Dissociation
Detoxication, chemical reactions	pH
	pK
Ionic organic mechanisms	
	Reaction rates
Isosterism	
	Dipole moments
Resonance	
	Redox potentials
Stereochemistry	

Certainly other topics can be added to this list but it is felt this material supplies a desirable nucleus to build upon.

The question now arises, "How far can one go or how far should an instructor go in presenting basic aspects to a student in medicinal products course?" It is my opinion the separation of basic concepts from the applied portion of the course is a mistake. A discussion of pKa is less effective when given as an isolated topic

than when this concept is applied to an interesting series of drugs such as the tetracyclines. Carbonium ion theory is interesting but more meaningful when utilized to explain ether formation in a discussion of general anesthetics. One should include those basic aspects which will explain and clarify the material given, thus providing a firm foundation for the student to use throughout his career. I certainly do not wish to be so presumptuous as to say my approach alone is the one to be used but in such a controversial subject as organic medicinal chemistry, basic concepts should be stressed certainly not as a separate portion of a course but as an integrated portion of drug action, physical behavior, synthetic procedures, etc.

The time of introduction of certain concepts into the course will vary with the manner in which the course is given. Some instructors prefer to follow a functional group classification of the course material, others prefer a pharmacological topic outline, while still a third group profess a mixture of the previous two methods to be the best. In any of these presentations some of the basic material will be used constantly throughout the course and should be introduced early while some material will fit one given topic and should be emphasized at that point.

Probably the most important single tool in understanding chemistry and the most neglected in a study of organic medicinal chemistry is the periodic table. It gives the answers to a variety of different questions and affords us a logical basis on which to establish part of our syllabus.

PERIODIC TABLE OF THE ELEMENTS

Group Period	I	II	III	IV	V	VI	VII	0
1	H							He
2	Li	Be	B	C	N	O	F	Ne
3	Na	Mg	Al	Si	P	S	Cl	A
4							Br	
5							I	

To illustrate the use of the periodic table of elements assume we are talking about the uses of trichloro acetic acid in the removal of warts or in dentristry for the sluffing of gum tissue. The instructor may remark that trichloroacetic acid is as strong an acid as hydrochloric acid. Why? Acetic acid certainly can not be used in the treatment of keratosis and acetic acid itself is known as a weak acid. Or maybe the topic is the chemistry of chloral hydrate. The instructor discusses its synthesis and the fact that chloral forms a stable hydrate. Why? We know other low molecular weight carbonyl compounds do not form stable hydrates. Allow me to develop a simplified presentation, more brief than would be given in the class room, concerning the first of the above questions.

If the medicinal products course is given in the junior year, it is safe to make the assumption that the students need to be refreshed in the use of the periodic table. For a discussion of modern organic chemistry it is necessary the student be familiar with the position of the elements in the first few periods. The student can easily master these few elements if a suitable mnemonic is given for the periods to be covered.

A covalent bond, as the student has learned in elementary organic chemistry, is a bond formed when two atoms share electrons equally. An electron can be depicted as a negative pole of a magnet held in position in its orbit by its attraction to the positive pole (the nucleus) and other forces which we won't consider. As we increase the positive charge on the nucleus, the electrons are pulled closer to the nucleus. Therefore within a given period, as we move from left to right, the valence orbit becomes closer to the nucleus (the atomic radius decreases.) Thus if a covalent bond exists between two atoms such as carbon and fluorine, the simplified picture would have the electron concentration greater at the flourine and we use the following notations to depict this

$$\overset{\delta+}{C} \;:\overset{\delta-}{F} \qquad \overset{\delta+}{C}\!\rightarrow\!\overset{\delta-}{F} \qquad \overset{\delta+}{C} \quad \overset{\delta-}{F}$$

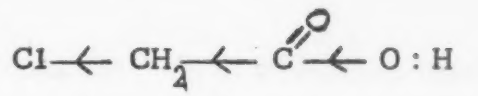
It can be seen that we have established a dipole. This uneven distribution of electrons in a covalent bond is referred to as permanent polarization and it is responsible for what the organic chemist calls inductive effect.

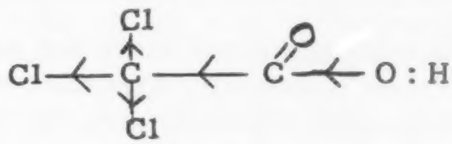
C : H	standard
C : X	electronegative-electron attracting
C: X	Electropositive

As we look at the periodic table it is easy to explain that the increase in nuclear charge gives a greater electron attracting effect as we proceed from left to right across the chart. The distance of the charge from the bonding electrons increases as we descend a given group. Since the attraction of the nucleus for a negative charge is inversely proportional to the square of the distance, electronegativity decreases as we descend a specific group to an element of higher atomic number. Since Chlorine is three groups to the right of carbon and only one period below carbon it is evident chlorine is electronegative with respect to carbon. In a carbon-chlorine covalent bond, carbon will be positive and chlorine negative. Establishing a basis for the inductive effect, we now use permanent polarization as an explanation of the great acidity of trichloroacetic acid.

IONIZATION CONSTANTS

	K	pKa
CH_3COOH	1.753×10^{-5}	4.76
$ClCH_2COOH$	1.396×10^{-3}	2.86
$Cl_2CHCOOH$	5.0×10^{-2}	1.30
Cl_3CCOOH	1.3×10^{-1}	0.89





It is apparent the effect of the electric dipole between carbon and chlorine will be felt upon other atoms attached to the carbon. The greater the electron attracting forces of the groups attached to the carbon, the greater the acidity of the carboxylic acid.

We can apply this same argument to the stability of chloral hydrate. Thus in a short discussion of the periodic chart we have reviewed or illustrated for the first time, inductive effect (permanent polarization), the concept of a dipole, and ionization constants of acids.

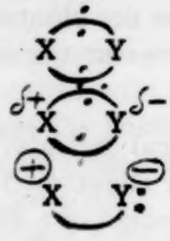
Now that we have introduced the basic concept of the covalent bond polarization we can use it in the discussion of many topics. An important concept in a course in medicinal chemistry is that of solubility. If the lecturer is giving material on the antibacterial effects of primary alcohols and wishes to present physical aspects, he can use bond polarization to explain association of liquids and thus explain the solubility of the low molecular weight alcohols in water and other hydroxylic solvents. In a molecule having permanent polarization, increasing the non-polar portion of the molecule, by increasing the number of carbons in a side chain, will produce definite physical changes in the molecule. The solubility in water decreases, the partition coefficient increases, surface activity increases, and many other changes occur. All these can be explained on the basis of the ratio of the polar portion of the molecule, to the non-polar portion of the molecule. This same effect can be related to Meyer-Overton theory.

Isosteres, a concept used in structure-activity relationship studies, are generally defined as compounds having similar electronic structures and molecular shapes. A study of atomic structure based on the periodic classification of the elements can lead to a firm understanding of isosterism. A facile example is the relationship of sulfur and oxygen. In water the existing bond angle is approximately the same as that in hydrogen sulfide. The electronic structure is similar, as sulfur is in the same group as oxygen and one period below it. Because of this similarity it is possible to interchange sulfur and oxygen in some physiologically active compounds. Compounds in this category are known to be bioisosteric.

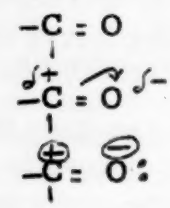
	Isostere S	Isostere O	Physiological Action
1.	Biotin	Oxybiotin	same
2.	Thiobarbiturates	Barbiturates	similar
3.	2-(2-Thienyl)-4-carboxy quinoline	2-(2-Furyl)-4-carboxyquinoline	similar (analgetic)

Isosterism will be utilized continually in the discussions of medicinal agents and if emphasized early in the course will allow the student to draw many analogies.

Resonance is another important factor which can be explained on the basis of the periodic table. Whenever electrically dissimilar atoms are connected by a double bond there will be a contribution of a structure apparently formed by one of the bonds (σ) remaining intact and the other (π) acquiring a certain amount of partial ionic character. The following is valence bond notation:



1. Normal
2. Resonance Hybrid
3. Extreme, Ion Pair Form



Since oxygen is to the right of carbon it will be more electron attracting in the carbonyl double bond and the resonance hybrid will exhibit the dipolar form shown. This concept and related mechanistic aspects make drug synthesis a much more systematic study. For example, a reaction of a grignard reagent with a ketone can be given in the following manner.

We have established a format for future similar reactions. Numerous examples of the above type can be given and other reactions based on ionic organic mechanisms can be introduced in the course.

Resonance is associated with numerous chemical, physical, and structural properties of molecules and thus is associated with biological action. Resonance has been shown to affect reaction rates, acid and base strength, redox potential, dipole moment, etc., therefore, it can be discussed along with biological action involving any of these physical aspects.

Many more facts can be related to the periodic table with a little effort on the part of the instructor.

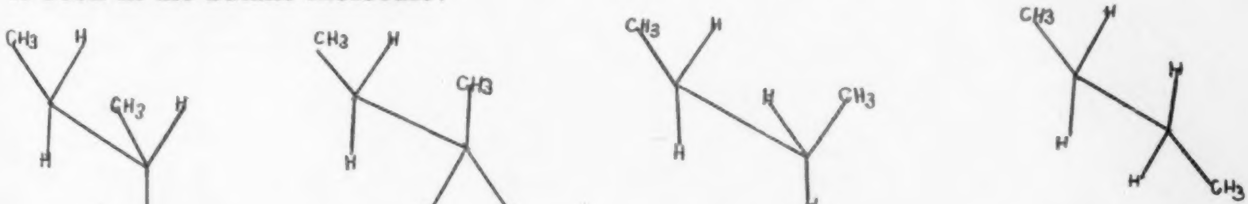
One of the most important factors to be brought forth in a medicinal chemistry is drug stability in vitro. A discussion of reaction rates in a course prior to the students having physical chemistry is time consuming and laborious. However, it is impossible to treat drug stability without discussing rates of reactions. Here again if the discussion on rates is presented along with the material on specific groups of drugs we can use relative decomposition under a given set of conditions. This will allow us to circumvent a detailed treatment of first and second order rates. If the lecturer is discussing decomposition of local anesthetics in aqueous solution he can point out that anesthetic A will decompose in five to seven days at room temperature at pH 10 while anesthetic B can be sterilized by boiling at the

same pH. In the synthesis of a sulfa drug the relative rate of hydrolysis of an acetamido group compared to a sulfamido group is easily indicated. Such relationships are fixed more firmly in the mind of the average student than a numerical rate constant.

Oxidation-Reduction Potentials are significant in the presentation of physiological action of drugs. The body is well supplied with such compounds as ascorbic acid, thioctic acid, cysteine, etc. The interaction of a drug with a compound of higher or lower potential, depending on circumstances, may modify the drug. It is well known that redox potentials are of significance in the study of the reversible enzymatic reactions. Thus a discussion of antioxidants in vivo or in vitro can be based on a simple introduction to redox potentials. Again the mode of usage of this concept would be determined by courses which have preceded the medicinal products course.

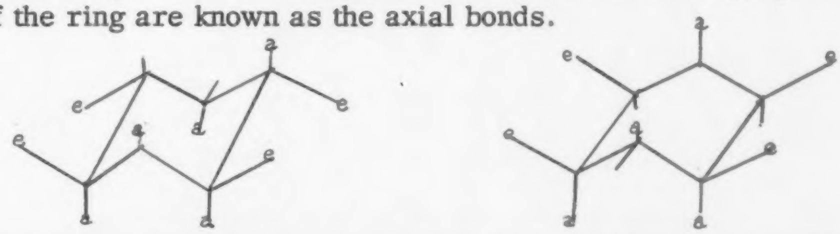
A very difficult concept to deliver in organic medicinal chemistry is the roll of stereochemistry in drug action, hence in most courses it has been neglected. Questions such as, "Why is d-amphetamine so active in comparison to the l-isomer?" and, "Why is ψ atropine inactive as a parasympatholytic while atropine is active?" can only be answered on a hypothetical basis. However, the answers are in the near future and the fundamental concepts should be given to the student in order to prepare him for data which he will receive after he has completed his formal academic training.

The systematic study of the stereoproperties of a molecule is known as conformational analysis. It is a tool which will aid researchers, teachers, and students alike in the understanding and depicting of drug shapes. The simple concept arises from the fact that there is restricted rotation about a single bond, thus giving a preferred conformation to a given compound. A simple illustration is seen in the butane molecule.

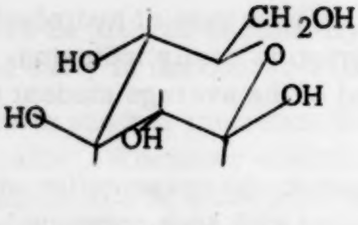


Full Eclipse Skewed Partial Eclipse Staggered

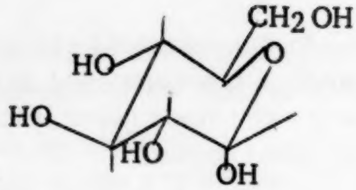
In a cyclic system we find a more fixed conformation. The bonds which are in the plane of the ring are called the equatorial bonds and those perpendicular to the plane of the ring are known as the axial bonds.



With this type of structure it is easy to show such phenomena as mutarotation in glucose as a reasonable occurrence rather than as a definition to be memorized.

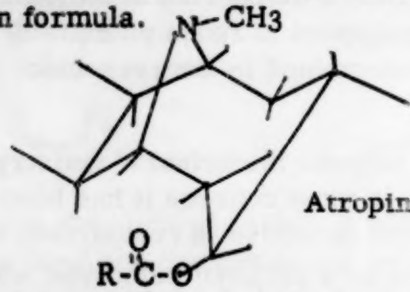


β - D - glucopyranose

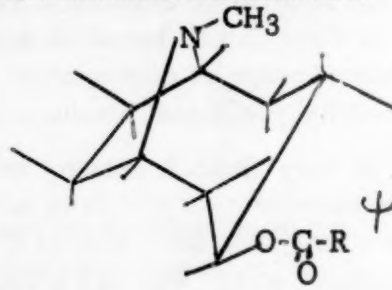


α - D - glucopyranose

In writing a structure for atropine, the relationship of the nitrogen to the ester oxygen is more realistic in the three dimensional conformational notation than in a projection formula.



Atropine



ψ-Atropine

With a few simple examples the student soon becomes familiar with both methods of writing the structures. The conformational method approximates the use of molecular models in the discussion of certain drugs.

Beckett's work on the relationship of structure to activity in the analgesic field is based on a conformational approach and has proven very fruitful. There is no doubt that this type of reasoning will be applied to other physiologically active systems and drug design will be placed on a more sound basis that it is at present. The student should be aware of such advances in his field.

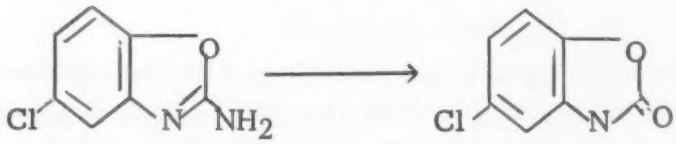
The effect of epimerization should also be emphasized each time it is met. In a discussion of the synthetic aspects of chloramphenicol it can be pointed out that diastereoisomers are formed and only the compound of a particular configuration is active. Many examples of this type can be presented and give the student a more realistic feeling for optical isomerism.

It is realized one can spend too much time discussing a topic such as stereochemistry. If so, there will be too little time in the course to cover the applied material. However, this is a matter of organization and should be fitted to the individual course and lecturer.

The nomenclature which is associated with stereochemistry, as well as general nomenclature, should be presented to the class. As an example, much of the trade literature involving steroids will use such simple terms as alpha or beta in the nomenclature. This terminology is of no meaning unless the student realizes it is a stereo notation. The student should be well indoctrinated in the use of drug nomenclature in general and should be made to realize he will have inquiries along this line.

The chemical alterations a drug undergoes in the body is a prime topic in medicinal chemistry. This topic as much as the preceding ones is of much more significance if treated along with a given group of drugs. The fate of a drug in the

body is often a lead to a new drug. 2-Amino -5- chloro benzoxazoline in the body is transformed to 5-chloro benzoxazolinone which is an active muscle relaxant. If the benzoxazolinone is given as the drug it is more effective.



Of course the chemistry of detoxication will be given in the biochemistry course but probably with different emphasis.

The topics and the method of presentation in an organic medicinal products course can be varied to a great extent. My main thesis is that . . . Basic concepts should be emphasized. These concepts should not be presented as addendums to a main portion of the course or as a preface to the course but along with the main body of the course material.

DISCUSSION

In explaining electronegativity, Dr. Osol wondered if use is made of Pauling's electronegativity values along with the periodic table.

Dr. Smissman indicated that he mentions the tables, but it does not give the students the numerical values.

Dr. Osol pointed out the benefit of using the values in physical chemistry courses.

For his purposes, in teaching courses without physical chemistry, Dr. Smissman suggested that relative electronegativity values could be used.

Dr. Jorgensen pointed out that modern courses in organic chemistry, taught with newer textbooks, include the topics under discussion. Only a brief review may be required in preparing for a discussion of relationships between physical properties and pharmacologic activities in medicinal chemistry courses.

Dr. Smissman expressed the belief that the review is necessary with the usual class of students. A number of the topics are found in both the basic and applied courses. Some must be taken up for the first time in the applied course, e.g. conformation of sugar molecules, various ring systems, etc. Students enrolling for the applied course have variable backgrounds in basic courses, hence nothing can be assumed. Furthermore, it is not safe to assume that the basic organic course material is adequately retained.

Dr. Jorgensen commented that, in view of the purpose of the medicinal chemistry course, structure - activity relationships rather than synthesis should be emphasized.

Dr. Smissman agreed. Teaching basic concepts does not exclude presentation of physiological, pharmacological, and phytochemical principles. The integration of basic concepts and applications gives the students a different view, a realization of the utility of the material, an understanding that it is a foundation upon which they can build.

Dr. Stuart challenged the teaching of principles along with the applications and showed a preference for teaching principles first as a preliminary to discussion of applications, on the basis that "repetition is one of the R's of education." Dr. Smissman indicated that his one semester course was too short to permit such repetition, however desirable it may be.

PHARMACOLOGICAL ASPECTS OF THE COURSE IN ORGANIC MEDICINAL PRODUCTS

W. Lewis Nobles

One of the prophets of old wrote — and this lifts it out of context — "your old men shall dream dreams and your young men shall see visions." It is most important to recognize that the Holy Writ did not obligate young men to see the vision! While many of my remarks may appear to be visionary — and many of them undoubtedly are — I sincerely trust that you will not be altogether the loser with respect to the time spent in listening to the remarks that shall follow.

I fully realize that I shall commit many sins of omission in this brief summary. In view of the incomplete status in which we now find many aspects of this topic, I can only express the sincere hope that one day the fabric of concepts in this field will not be woven of a plethora of woof with a paucity of warp, but will be strong and solid.

The undergraduate course in organic medicinals should, among other things, comprise a study of the sources, methods of synthesis and/or procurement, nomenclature, significant physical and chemical properties, mechanisms of action, structure-activity relationship(s), and uses of the organic medicinals. The question may be raised as to whether or not it is desirable to cover these and related topics in one course. This is merely academic; the pharmacy student must gain an intimate knowledge of these and many other related items. Nonetheless, the results should be achieved by education, rather than indoctrination. The unimaginative, encyclopedic retention of all the above information as isolated facts does not constitute a usable knowledge of organic medicinals. In Life magazine Charles Van Doren, of TV fame, presented a searching challenge along this line. Van Doren concluded, after careful thought about his experience, that a contestant could answer every question ever asked on all quiz programs and still be a nincompoop. He could "know everything" and still know nothing, because he knew none of the connections between the things that he knew. This is the chief goal of learning -- to be able to tie things together into a meaningful whole.

There is really only one safe way to avoid making mistakes: to do nothing or, at least, to attempt nothing new. This may well, however, be the greatest mistake of all!

It is my assigned task to discuss the pharmacological aspects of organic medicinal chemistry. The acceptance of this aspect in various courses being offered will undoubtedly vary from nil to such an over exhuberance concerning various pharmacological phenomena as not to allow for a clear presentation of the chemistry involved.

In my remarks and in the syllabus attached, I shall follow a pharmacological classification of the drugs. There are honest differences of opinion on this point; actually, either method appears to involve some of the other. Thus, a dual system is almost inevitable.

For any given class of medicinals, the following points may be considered:

I. A description and discussion of this pharmacological category.
II. Structures within the class based on a chemical classification. and structure-activity relationships
III. Synthetic schemes by classes
IV. General comments on the class of agents
V. Discussion of Individual Compounds
   A. Generic Name
   B. Synonyms
   C. Chemical Name
   D. Structure
   E. Solubility and physical properties -- relate these aspects to dosage forms, compatibilities and incompatibilities
   F. Therapeutic use and dose

The pharmacological aspects are thus summarized generally; a specific breakdown in the form of a syllabus is attached to this paper.

The proper presentation of the chemistry of organic medicinals should provide a firm basis for the integration of basic facts already accumulated; no text in medicinal chemistry can be a primer; it is a "part of all that it has met." This course should allow for the correlation of the known with the unknown and for the expression of original thought in the broad vistas of the unknown!

Since approximately 90% of our students find employment in some aspect of retail pharmacy, the scope of this course must take into consideration how the future retailer may best use the material that is presented to him. The retail pharmacist is quite often the most scientifically trained person with whom the public comes into contact. It is largely through the pharmacological aspects of the newer drugs that areas are opened up for the exercise of his judgment. This is utilized in:

1. Filling prescriptions -- not "how" but "why"
2. Detailing physicians -- quite often informally over the telephone
3. Serving as a liason between the physician and the public
4. Advising the public concerning new products -- particularly those non-legend items that are over-enthusiastically promoted by the lay press, radio and TV

The pharmacologist has the responsibility of correlating the work of the organic chemist, who has made the new compound, with that of the clinician, who wishes to use it in human therapy. The unique position of the pharmaceutical chemist should be recognized and no aspirations of complete autonomy with regard to chemistry or pharmacology should be sought.

As the five year program becomes standard, certain changes from the older pattern will undoubtedly be seen. In the four year program, organic medicinals could only be presented in the third or fourth years, after elementary organic chemistry. If presented in the third year, it was then necessary for this course to be given concurrently with anatomy and physiology or physiology. In the five year program it would appear to be very desirable for the course in organic medicinals to be given either in the fourth or fifth years. If it is given in the fifth year, and a pharmacological classification is used, close correlation between this course and pharmacology should be achieved by the faculty involved. It would be my personal preference that this course be given in the fourth year, thus serving as a strong bridge between organic chemistry and physiology on the one hand and pharmacology on the other.

Certain pharmacological aspects appear to require rather vigorous emphasis, and not by the rather dogmatic transcription of much tabulated data from the blackboard -- or even slides properly prepared! The most important areas are:

1. What constitutes a specific pharmacological class of drugs
2. How and why a given drug is thus classified
3. Some of the gross aspects of the action of the drug in the body
4. Mechanism of action
5. Structure-activity relationships
6. Absorption, fate and excretion
7. Dose and use

An adequate description of the mechanism of action is essential to an understanding of why the drugs we have are useful.

Structure-activity relationship logically follows the above and must be somewhat limited in scope at the undergraduate level. Nonetheless, the student should get a reasonably clear picture of this concept as it applies to useful medicinals. While it is true that most structure-activity relationships have been retrospective, it is equally true that this line of approach has contributed much to the elucidation of our current knowledge in this field. Ever since Crum-Brown and Fraser (Crum-Brown, A. and Fraser, T.R., Trans. Roy. Soc. Edinburgh, 25, 151(1868-1869)) expresses the problem of structure-activity relationship (SAR) in the form of a pseudo equation, $\phi = f(C_D)$ it has exercised and is exercising the minds of many people. This concept has served as a magnet to attract the attention and absorb the energies of chemists and pharmacologists. In this area it is dangerous to generalize and anomalies are common; nonetheless it is a vast domain which constantly beckons the inquiring mind. The lack of currently available structure-activity relationships in some areas should also be pointed out. Such a schism between the known and the unknown suggests that some basic information is missing. Thus, inquiry into this duality of knowledge and ignorance is urgent and imperative.

The topics of absorption, metabolic fate and excretion might best be considered under the physiological chemical aspects of this course. Martin (Martin, G., "Biological Antagonism," The Blakiston Co., New York, 1951, p. 477) suggests the relationship of biochemistry to pharmacology is that of natural biological antagonists to synthetic antagonists. Nonetheless, it would appear that marked elaboration on

these points should be reserved for consideration in the course in pharmacology. Particular emphasis should be placed on these aspects in the course in organic medicinals when they have been involved in the development of a drug (Meprobamate from Mephenesin) or when the metabolic transformation product becomes as important -- if not more so -- than the parent compound.

Such aspects of chemical and pharmacological knowledge should be integrated in the course in organic medicinals in a manner that is optimum for training in this unique, borderline area. If we are to extend the frontiers of our knowledge in this area, we must enlist the interest and enthusiasm of an ever increasing number of well-trained investigators. This requires students of high calibre. I believe there is no better way to fire the spark of creative interest than to present a brief look into the dynamic aspects of organic chemistry from the viewpoint of biochemical pharmacology.

In conclusion, I should like to paraphrase the remarks of Szent-Gyorgyi (Szent-Gyorgyi, A., "Bioenergetics," Academic Press, New York, 1951, p. 140).

The pharmaceutical chemist, venturing into this field, can only do so at the danger of errors, many of his interpretations being found at fault later. He can only hope that through the door, left ajar, students will follow who are more qualified to deal with the problems. His only reward will be the fleeting glance at a future researcher, from the elevation of which the letter - dash - letter symbols (such as are used for a high energy phosphate bond) will look like skeletons which can tell us no more about the real nature of life than the fossil bones of a dinosaur can tell us about that animal's reflexes or sexual relations.

To this objective -- our research and teaching should ever be dedicated!

DISCUSSION

Dr. Doorenbos mentioned that the topics included in this course were presented in the first six weeks of his course in organic pharmaceutical chemistry. Knowledge of these basic concepts facilitated the students' understanding of the material presented later in the course.

Dr. White pointed out that most teachers do not have the opportunity for such an extensive course as that proposed by Dr. Lee. An exchange of ideas on presentation of basic concepts necessary for an understanding of such phenomena as biological antagonism, mechanism of cholinergic or anti-cholinergic activities, is justified.

THE INTERACTION OF DRUGS AND BIOLOGICAL SYSTEMS

Kwan-Hua Lee and John J. Eiler

For some time we have offered a course attempting to present some of the facts and concepts that are involved in understanding the interaction of drugs and biological systems at the molecular or quasi-molecular level. Until recently the course has been available only to graduate students in pharmacology and pharmaceutical chemistry. With the adoption of the new program of education offering four years of instruction in the professional area, a similar course was made available to the undergraduate student of pharmacy in his senior years--the sixth year of collegiate education.

The incentive to develop these courses, graduate and undergraduate, arose out of the desire and need to bring together in some more organized fashion much of the material pertaining to the biochemical action of drugs presented elsewhere in the standard curriculum. However, in developing the two series of lectures, we have been guided by the view that any systematic presentation of the interaction of drugs and biological systems must transcend the restrictions imposed by the biochemical viewpoint, if that viewpoint is interpreted to place a limitation on thinking beyond the molecular level.

Due to the interdisciplinary and polemic nature of the material covered, the undergraduate course has presented problems in pedagogy that were not quite so apparent in the course for graduate students. To a significant degree undergraduate instruction is compartmentalized and non-polemic, with each compartment represented by a field and with each question accompanied by an answer. As pointed out by David Riesman, each field "embraces a series of intellectual tracks down which we run, protected by our lines from having to look in too many directions at once." To consider the concepts pertinent to an understanding of molecular pharmacology or the biochemical action of drugs, it is necessary to look in "too many" directions at once and to be satisfied with less than unequivocal answers. To evaluate the contributions, both real and supposed, of the antimetabolite theory, for example, it is necessary to consider the literature in general biochemistry, general pharmacology, enzyme kinetics, structural organic chemistry, cell physiology, etc. and to have a concern with biological forms in addition to the mammalian.

Before considering the nature of the material presented in the undergraduate course, it is well to point out that the students come to the course after having had instruction in zoology, anatomy, physiology, biochemistry, microbiology, organic and physical chemistry, a year of calculus, pharmaceutical chemistry, pathology, and pharmacology. Use is made of their information in each of these fields.

For the purpose of discussing the contents, we may divide the course into three sections, each with subsections. In the first section, we consider the factors that control the concentration of drugs at the sites of action. In the second, the student is given the opportunity to consider more thoroughly than elsewhere in our curriculum the possible nature of the drug receptors and the types of interactions that may be expected between drug and receptor. In the final third of the course, the biological and biochemical actions of two classes of drugs are considered in some detail. Also included in this section is a discussion of those studies in drug resistance which contribute to our knowledge of the mode of drug action.

SECTION I

The student is first reoriented with respect to the factors which influence the intensity and the duration of the action of drugs, especially when the drugs are administered to the higher animal forms. Emphasis is placed on the physical and physico-chemical factors which determine the concentration of drugs at possible sites of action. Brief consideration is given to the significance of drug transport, distribution, and excretion in determining effective drug concentrations. The role of lipid as a storage site is emphasized; inert protein binding is considered. The nature of the transport across membranes is considered and examples of active and passive transport are given. Examples are chosen from each of several types of cell membranes. The material is presented to the student with the thought of focusing attention on two inter-related aspects of the importance of physical properties. In the first place, he is given sufficient information to appreciate the significance of the physical properties in influencing the intensity and duration of action of drugs. Secondly, he is led to appreciate the problems involved in drawing conclusions regarding the relationship of structure to pharmacologic activity from studies involving the intact animal.

Enzyme reactions which promote the chemical transformations that lead to enhanced rate of excretion (generally) and to reduced biological activity (frequently) are considered only briefly. We have found it necessary to give only sufficient of this material to insure that it is assigned a proper place among the other factors controlling the concentration of drugs. The student has already been given the enzymic aspects of "detoxication" in the course in biochemistry. The courses in pharmaceutical chemistry have emphasized the effects of the structural changes on the rates of transport and excretion and upon distribution within the body.

Many of the ideas and concepts considered thus far have already been given to the student in other courses earlier in the curriculum. Frequently, however, the ideas are presented only as "bits and pieces" ancillary to the subject matter of the earlier courses. As a result, the student often lacks the understanding which may be acquired through the presentation of the facts and ideas apart from other considerations. Further, the recent developments in this field are sufficiently impressive and important to warrant a more extensive treatment even than that given by us. We are to learn about some of these developments later in the week from Dr. B. B. Brodie who has made many significant contributions in the field.

Advantage is taken of the material presented thus far to provoke similar thinking with respect to the action of drugs on single cells. To this end, we have found it necessary to review briefly the chemical and physical anatomy of the cell and to present several aspects of cell physiology. The chemical and physical aspects of cell compartmentalization are given in moderate detail. The composition and function of the cell membrane are discussed at a level beyond that encountered in standard texts. The evidence in support of the presence of enzymes on the cell surface, as possible drug receptors, is presented.

The cell is then considered from the point of view of the possible sites for drug action. Much of the material for this part of the course is drawn from Clark's monograph and brought up to date, to the extent permitted by our scholarship, through use of material in the more recent literature.

While it may appear that our approach is suited only to the graduate student, we have found that the undergraduate, to a gratifying extent, both understands and appreciates the possible significance of the material presented. The simple but ingenious experiments by Marsland, making use of a drug dissolved in an oil droplet, to determine the site of action of narcotics, have challenged several groups of students to explore the literature on their own. Likewise, the presence of enzymes on the cell surface seems to have a stimulating effect on students whose instruction in pharmacology has pointed to the cell surface as a possible receptor site.

SECTION II

This phase of the instruction is concerned with the possible nature of the receptor site and with the kinds of interactions that may be expected among metabolite, receptor and anti-metabolite. Since enzymes figure so prominently, but not exclusively, in any consideration of the receptor, we attack the problems in this area by first considering the nature of the globular proteins, with emphasis on the number and kinds of reacting groups present. The qualitative aspects are integrated with estimates of the magnitude of the equilibrium constants expected from various types of bonds. Use is made of the literature in enzyme chemistry to present pertinent examples. The viewpoint thus established is carried over to a consideration of the concept of active centers on enzymes. The poly-affinity concept is presented with suitable examples. The action of several types of inhibitors is considered in moderate detail with respect to the chemical interaction between the inhibitor and the enzyme. The inferential data regarding the nature of the active site is worthy of presentation in the case of a few enzymes, especially so in the case of acetylcholine esterase.

With this background, the student has an intellectual appreciation of the Michaelis-Menten formulation which goes beyond the algebraic derivation. More pertinently he has a greater interest in the various formulations for the kinetics of inhibition of enzyme catalyzed reactions. The generalized theory of Straus and Goldstein is accepted with understanding, providing it is not made an exercise in mathematics.

Almost by definition, the heart of molecular pharmacology lies in an understanding of drug-enzyme, or at least drug-receptor, interactions. The concept of competitive inhibition, first given pharmacologic vitality by studies on the sulfonamides, has given great stimulus to the search for drugs that will unite with receptors. However, the therapeutic successes resulting from the application of the principle have been meager. In presenting the various types of drug-receptor interactions, with examples drawn from the biochemical and pharmacological literature, both within and without the field of chemotherapy, it is necessary to keep in mind the marked difference between the hope and the fulfillment offered by this concept. In attempting to develop the background necessary to place the concepts and formulations in proper perspective, we have drawn upon the biological literature in a manner not simple to present here. Some consideration is given, for example, to the uniqueness of biochemical identity (host versus parasite; one tissue versus a second) and the possible influence of physical factors.

The example presented by the sulfa drugs is a good one with which to review the question of selective toxicity. The fact that para-aminobenzoic acid is a metabolite for some organisms but not, apparently, for man demonstrates one aspect of selective toxicity. The additional observation that the folic acids in man and unicellular organisms may differ adds subtlety to the concept. Indeed, time permitting, a more or less complete development of the pictures concerning the possible mode of action of the sulfa drugs is a profitable development.

One cannot hope to cover even a fraction of the various types of drug-receptor interactions that have been proposed in the pharmacological literature. Even the few that may be given present the problem of avoiding the aggravations inherent in the algebraic formulations. Non-competitive reactions are covered in some detail. While the number of examples, outside the field of chemotherapy, that can be given is small, the student is given to understand that at the present time we know little about the enzymes responsible for the action of the tissue specific drugs, so little in fact that some investigators view with skepticism the cardinal role of enzymes in explaining drug action. Competitive inhibition is covered, again in moderate detail, drawing upon examples both within and without pharmacology. Some of the vitamin analogs afford examples that illustrate several points of potential interest to the student. The uncompetitive interaction is presented only to demonstrate that the systems can and do become complicated. Synergistic interactions are mentioned briefly. The relation between each of these interactions and the common types of concentration-action curves are demonstrated.

Because of its pharmacological pertinency and its biochemical value, we spend some time in considering the interactions of acetylcholine, the esterase and the inhibiting drugs. The detailed information available permits us to draw together in a practical way many of the points made earlier. The action of the nerve gases is included.

Advantage is taken of some of the biological results presented in this section to draw attention to the differences between the action of drugs under equilibrium conditions and the time-dependent actions. Even at this late date in their collegiate

careers, students have difficulty in making a distinction between equilibrium and non-equilibrium conditions. However, it is not difficult to find investigators who are not careful about the distinction.

SECTION III

In the final section, we have elected to consider in some detail the biological and biochemical actions of two classes of drugs for which well documented data are available. The studies of Clowes and coworkers on the substituted phenols, as extended by modern biochemical research, have permitted the development of considerable insight regarding the biological action of this group of chemicals. In studies on the eggs of the sea urchin, the biological effects relating to cell division and respiration have been charted in some detail. Studies are available which purport to establish the differences in biological action of the ions and the undissociated molecules. Inherent in these studies are possibilities for analysis of structure-action relationships.

The value of this group of drugs lies in the fact that, relatively speaking, considerable information is available both with respect to their biological action on the human being and on simple forms and with respect to their biochemical action at a subcellular level. Although never established rigorously, there is good reason to suppose that the drugs exert their characteristic biological effects by uncoupling phosphorylation for the associated electron transport. This view has served as a prototype for the explanation of the action of other tissue specific drugs, but never satisfactorily. The studies in this area are treated in a way that focuses maximum attention on the more general aspects presented earlier in the course. This part of the course necessitates the presentation of new material both in biology and biochemistry.

A similar treatment is accorded the group of agents classed as narcotics. We have felt the need for the student to understand the experimental background and results of the early workers who related narcotic action to lipid solubility. The experimental results and the views developed under the heading of the Ferguson principle are considered in somewhat greater detail and from a different viewpoint than is given in the standard texts in pharmaceutical chemistry. The effect of selected narcotics on biochemical systems is considered rather extensively. The effects on electron transport versus the effect on energy utilization are weighed and related to the many excellent studies in neuro-pharmacology. An attempt is made to correlate the various findings in a manner that is difficult to encompass in a brief paper. In considering the substituted phenols and the narcotics, we try to present an overall view of the many problems that face the investigator who attempts to explain pharmacologic action on a molecular basis. The gulf between the molecular phenomenon and the associated physiological phenomena is still too great to be bridged except in an isolated instance or so.

In the final section, we consider some of the biochemical and biological phenomena involved in the question of drug resistance. This, we believe, is a fertile field for investigations leading to an understanding of drug action. Also, there is need for the pharmacist to have greater understanding of this field to

use drugs intelligently at the practical level. Many of the studies by Hinshelwood and others can be considered with great profit by those interested in molecular pharmacology and the biochemical interpretations of drug action.

Not all of the material we have discussed can be presented in the forty-five or so lectures at our disposal. Greater emphasis is given to different sections from year to year, permitting the instructors to increase their knowledge and organization of the material in the several fields as time goes on. Students use the excellent volume "The Basis of Chemotherapy" by Work and Work, and the monograph on "Selective Toxicity" by Adrian Albert.

During the period in which the undergraduate course has been in the process of development, we have been plagued with the fear of presenting material that goes beyond the needs, intellectual and practical, of the student in pharmacy. Our apprehensions have been reduced by the thought that a few of the concepts and ideas are actually new to the student. In one course or another he has made contact with each of the major concepts. The more extensive development which we accord to some of the ideas is justified, we believe, by the view that the pharmacist must become better informed in many aspects of therapeutics if he is to serve the members of the other health professions in some consultative capacity.

SYLLABI OF ORGANIC MEDICINAL PRODUCTS COURSE

Ole Gisvold

Phytochemical Aspects

Let us for the moment, take any organic compound that can be classified as a drug, whether it be found in any of the official compendia or not and outline the information that a pharmacist might be required or wish to know or be able to find. Such information might be applied directly in the daily practice of pharmacy, be considered as broadening the scope of knowledge in an area directly related to pharmaceitical interests or even serve as a background or prerequisite to certain courses given in the Graduate School. The following outline is used to emphasize the diversified amount of data that can be treated didactically in conjunction with any one organic compound used as a drug.

- Official Title i.e. Latin and English
- Official Synonyms
- Other Synonyms
- Definition (Official or otherwise)
- Source i.e. natural or synthetic
    - Isolation procedures
    - Methods of Synthesis
- Chemical properties
- Physical properties
- Drug development
- Chemical, physical, structural, conformational activity correlations
- Mode of action
- Pharmacological Activities
- Uses
- Modes of Administration
- Dosage forms
- Doses

Although a treatment of some parts of this outline, such as titles, official synonyms is quite limited, this is not true with other areas. The extent of the treatment of some areas of this outline may be limited by the credit value assigned to the course in question, the data in the hands of the lecturer, the data available in the literature, and the treatment of some areas such as pharmacological activities in other courses. The didactic treatment of all areas of the outline on this page for a single organic compound may entail a considerable amount of lecture time. If this is multiplied by the large number of organic compounds described in the official compendia, new and non-official remedies and other new and useful drugs, the amount would be very great indeed. With the rapid increase in the number of new organic drugs being introduced every year, the time factor becomes more important. It has been my experience that three quarters of lectures with a total of 10 quarter credits places limitations on the presentation of the subject

matter even though very little emphasis is placed on pharmacological activities and dosage forms.

Because of the time limitations placed on the presentation of the subject matter in this course, little attention is given to any special phytochemical aspects i.e. biogenesis, methods of isolation, purification or identification. Whether an organic compound is isolated from a natural source, a naturally occurring compound now prepared by synthetic methods or is a synthetic compound obviously does not alter its biological, chemical, physical structural or conformational properties. Therefore, from some aspects it is of little consequence to the practicing pharmacist, physician, pharmacologist, and medicinal chemists as to the origin of the drug in question. However, there are a number of other aspects that are more significant and of greater interest. One of these is the utilization of naturally occurring (plants or animals) compounds as very useful prototypes for the development of other useful drugs. If such an approach is adopted for the didactic treatment of plant (and animal products) it permits the initiation of a discussion of structural and conformational properties as they may have a bearing on their mode of action. This discussion canbe correlated with the chemical and physical properties that may serve to further explain the usefulness of the drug. In some cases these plant (and animal) drugs serve as an introduction to a certain class of drugs. A very familiar and excellent illustration is the use of atropine as a prototype for the development of many antispasmodic drugs. It is remarkable that this plant product has the requirements depicted in the following formula (Figure I) that enables it to block the activity of acetyl choline, a mediator of the parasympathetic nerve system. Scopolamine, although it has activities similar to atropine has central effects not shared by atropine. An examination of a molecular model of scopolamine as depicted by a conformational formula shows the similarity to atropine. The essential difference being the presence of an epoxide ring in scopolamine. One might conclude that the epoxide ring through its contribution to the physical properties of scopolamine might account for the difference in the activity of scopolamine versus atropine via drug distribution in vivo. The epoxide ring certainly offers no bar to structural or conformational requirements necessary for biological activity. The bicyclic structure of atropine and scopolamine forces a rigid conformation to the piperiding ring. This rigid conformation may play an important role in their biological activities. This may in part serve to explain why the esters of N-methyl-4-hydroxy piperidine are not as active as atropine and scopolamine. Another factor is the axial or equatorial position of the alcohol group of the base portion of the molecule. In tropine and scopine it is axial. In such drugs as eucatropine, the alcohol group of the substituted piperidine rings is probably equatorial. This may in part account for its difference in activity as compared to atropine.

Although many neurotropic antispasmodics and mydriatics not containing a piperidine ring have been synthesized their conformations are not restricted and hence probably their differences in biological activities.

Although the mode of action of morphine is still not known with certainty, sufficient advancements have been made in the area of analgesics to permit these data to be of instructional value in the presentation of analgesics using morphine,

a plant product, as a prototype. The use of conformational type formulas can serve to a very good advantage as the following can illustrate (Figure II).

The information depicted in Figure II represents a case of the cart before the horse, but, had man first solved the case of morphine, the example would have been similar to atropine versus many synthetic antispasmodics.

The illustrations cited by atropine and morphine in part also can be extended to the vitamins as illustrated by the vitamins K, D, and E.

The utilization of conformational formulae also can be used to very good advantage in the presentation of the subject matter of steroids even though there are more biologically active steroids that are synthesized by animals and in the laboratory than are elaborated by plants. The following conformational formulae (Figure III) are presented to illustrate some similarities and differences in some steroids of medicinal interest.

The four non-aromatic rings (three six-and one five-membered) when saturated may have the cholestane, coprostane or cardanolid conformations. The cholestane conformation is an all chair, all trans one. It is a long, thin, relatively flat molecule. The conformational formula, although not as effective or as accurate as a molecular model, serves to a much better advantage than the conventional type. When, for example one considers the α and β positions at a given carbon atom of the conventional type versus the axial and equatorial relationships depicted in a conformational formula. The fact that in hydrocortisone the OH at C_{11} must be axial for maximum activity might imply that this face of the molecule approaches certain biological sites in order to exert its activity. Assuming this to be the case one then readily could offer an explanation why so many modifications of the naturally occuring steroids are possible to produce large variations in their biological activities. Formula . A....... is presented to show some of the modifications that usually lead to increased activities. These increases in activity possibly may then be explained as follows.

1) Loss of CH_3 at C_{10} to yield the 19 nor compounds may permit a closer approach to the site where the molecule exerts its biological activity.

2) An equitorial CH_3 at C_6 might (1) furnish an additional binding surface (van der Waals forces) (2) add greater stability to the conformation of the molecule and (3) favorably alter the physical properties.

3) An axial fluorine atom at C_9 also might have multiple effects i.e. (1) favorably alter the physical properties, (2) add to the stability of the conformation of the molecule, (3) increase the acidity of the axial OH at C_{11} to favor greater biological activity through stronger binding properties at the site of activity.

Alkaloids, classically often have been grouped together because they usually are basic in character. Other than this one common property great differences exist in their structural, physical, chemical and biological properties. It is the latter difference that precludes the treatment of alkaloids as a separate group of medicinal substances. In a number of cases an alkaloid has been utilized as a prototype for the development of other synthetic drugs with the final objective of improving on nature.

The great differences in the structures of many alkaloids leads to the conclusion that probably there are many biogenetic routes to their formation. At the present time very little is known about the biogenesis of alkaloids as well as the biogenesis of glycosides, terpenes, etc. However, it is well known that species in a given genus and even related members of certain plant families produce the same or closely related substances. This might point out some common pathways of biogenetic origin. It also is interesting to note that some alkaloids such as the opium alkaloids, the curare alkaloids, etc. that are found in entirely unrelated families appear to have been synthesized by the plant via some common precursors. These precursors give rise to the presence of phenyl ethylamine, substituted ethylamine, phenyl ethane and substituted phenyl ethane. Para hydroxyphenyl ethylamine and 3,4 - dihydroxyphenyl ethylamine have been found in a number of plants. Even though these substances may not be the precursors, nevertheless for teaching purposes one can use this line of approach to simplify the presentation of the structures of some of the complex alkaloids such as d-tubocurare, morphine, etc. (Figure IV).

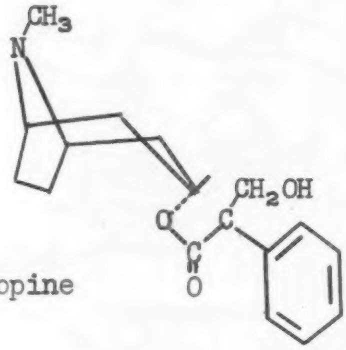
In the case of glycosides we again encounter a situation similar to the alkaloids. The only similarity in composition of these plant substances is the presence of a sugar residue. In the case of the better known O glycosides it would appear that the biological activity resides primarily in the aglycon portion of the molecule. This appears to be true in the well known digitalis glycosides, rutin, etc. The sugar residue, however, can exert a significant effect i.e. by its contribution to the physical properties of the glycoside. The resultant physical properties determine to a marked degree the absorption, distribution, duration of action, etc. of the glycosides. This does not imply that a sugar residue is a most desirable auxillary factor. Auxillary structures other than sugars might prove more desirable. This is an area where more research is needed.

The preceding examples illustrate in a limited way how the chemistry of plant products can be utilized in the area of the teaching of medicinal agents.

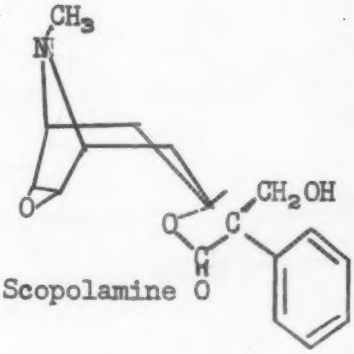
Before concluding this brief presentation it should be distinctly within the scope of this course to discuss the subject of metabolites versus antimetabolites. Many examples in this area such as thiamin versus pyrithiamin, pyridoxine versus desmethyl pridoxine, etc. could be cited. These represent examples where specific modifications are required. In other areas where the preparation of an antimetabolite is desired, more general lines have produced interesting results such as the substitution of a nitrogen atom for a carbon atom to yield the various aza analogues of the purines and pyrimidines. In the case of the amino acids general lines have been followed with the preparation of the -methyl, N-methyl, D-configuration, etc. to produce metabolic antagonists of the amino acids.

I want to thank the members of the program committee for extending me the invitation to speak before the members of this Teachers' Seminar. If in some way I have made a small contribution to the teachers in this area, I shall be satisfactorilly rewarded.

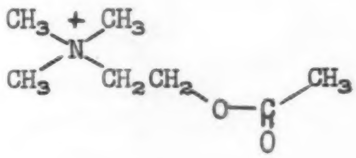
Thank you for your kind attention.



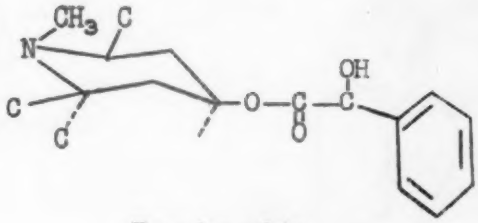
Atropine



Scopolamine

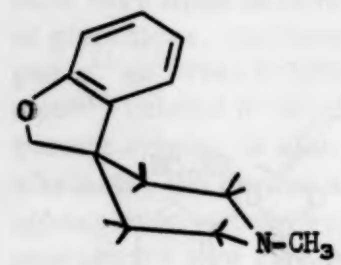


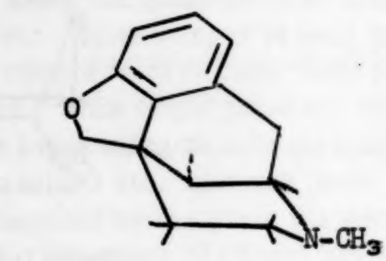
Acetylcholine

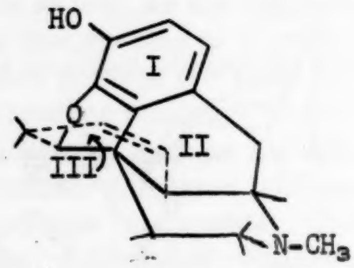


Eucatropine

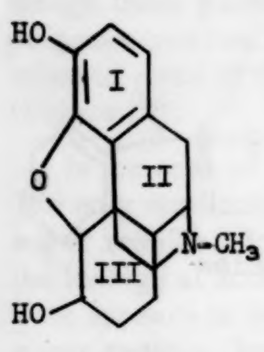
Figure 1



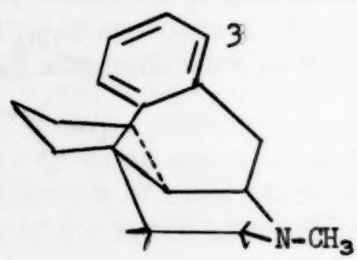




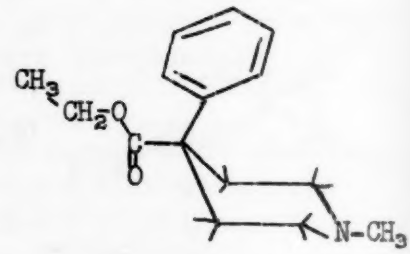
Morphine
(Rings II,III-Cis)

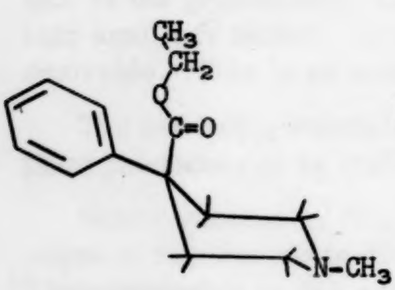


Morphine

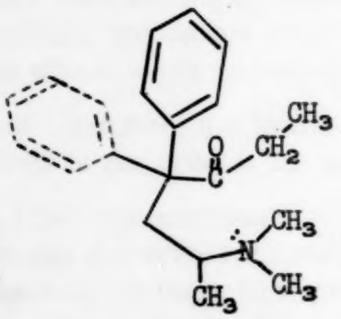


N-Methyl Morphinan
(OH at C-3 = Levo-Dromoran)

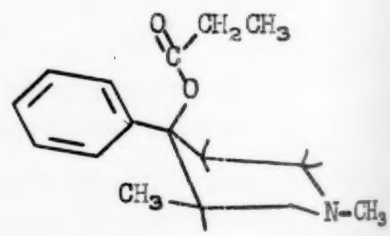




Demerol

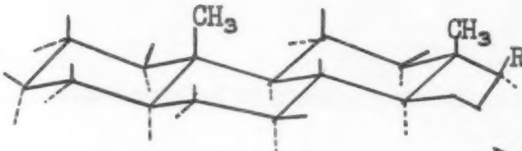


Methadon

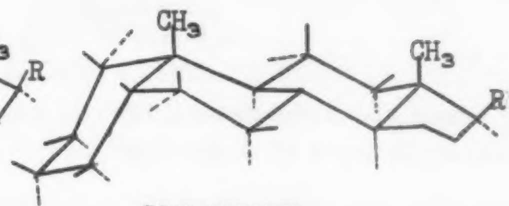


Prisilidine

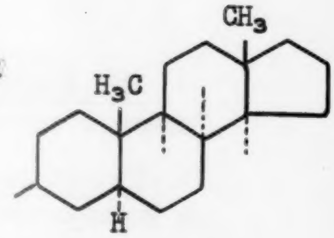
Figure 2



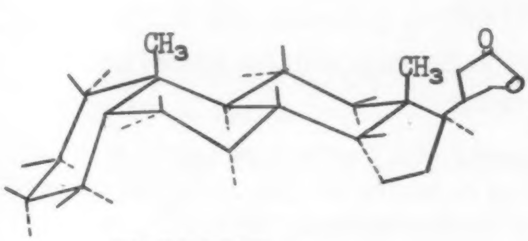
CHOLESTANE
(All trans)



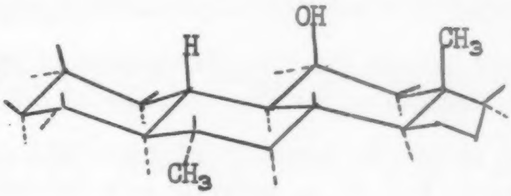
COPROSTANE
(cis, trans, trans)



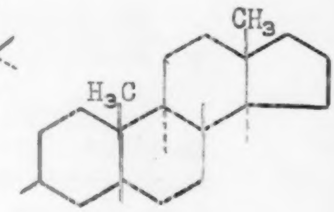
CHOLESTANE



CARDANOLID
or CARDOGENAN
(cis,trans,cis)

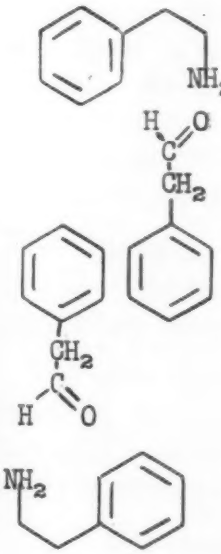


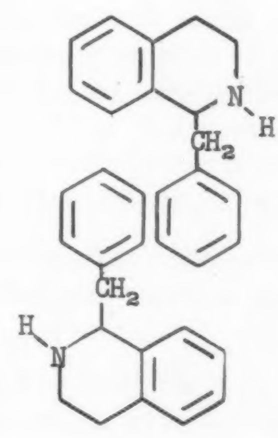
Formula A

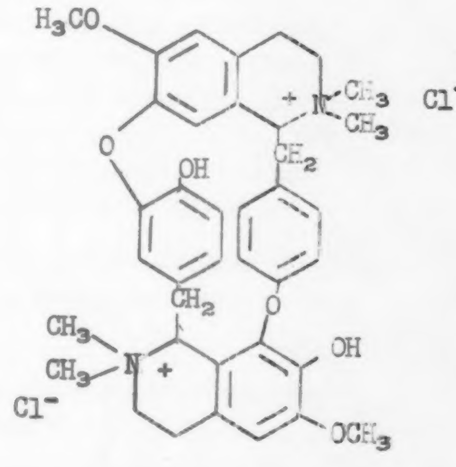


COPROSTANE
(cis,trans,trans)

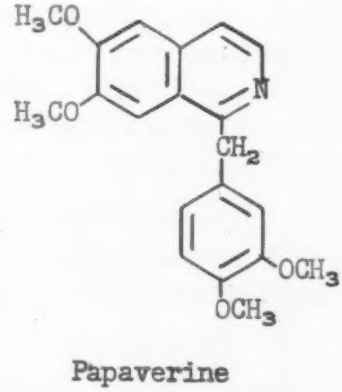
Figure 3



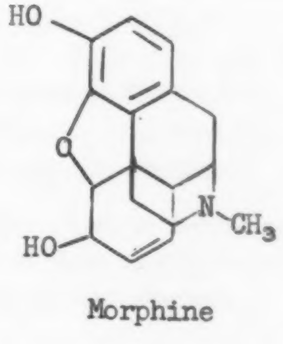




Tubocurarine Chloride



Papaverine



Morphine

Figure 4

DISCUSSION

Dr. Stuart asked about the desirability of supplying students in advance with sheets of partial structures of molecules.

Dr. Gisvold admitted that he had not employed this device, and agreed that it would expedite instruction.

Dr. Stuart suggested that the same objective could be achieved by use of a teaching notebook in which partial structures appeared.

Dr. Gisvold thought that the preparation of textbooks warrants the support of the American Foundation for Pharmaceutical Education.

Dr. Stuart raised the question of the establishment of a committee under the auspices of the A.A.C.P. to serve in a coordinating capacity for the contributions that could be made by the many teachers who have such problems.

Dr. Zopf stated that the A.A.C.P. could do this, but has never been approached. Any recommendations to the Foundation could be channeled through Dr. Webster.

INTERACTION OF THE STUDENT AND TEACHER IN THE LEARNING PROCESS

Milton O. Pella

Because we are all teachers we are concerned with the process and products of learning, the activities of the teacher during the process of helping students to learn, and the activities of students during the process of learning. That is, our concern is with learning and instruction.

Learning is the result of the interaction that accurs between the student and many other forces.

We must establish certain facts prior to delving into the main problem.

1. The students in the classroom are not the only learners and the teacher is not the only one from whom the student learns. There is little doubt but that more learning occurs outside the classroom than in and that students learn from each other, from books, and as a result of self discovery.

2. Learning has been considered as synonymous with memorizing or at best with the acquisition of knowledge or skill. These are, of course, legitimate forms of learning but are not the whole of it. In order for knowledge to be useful it must be understood. That is, it must have significance in the life of the learner. Facts, of course, are not the only desired outcome of learning. There are attitudes, interests, appreciations, and problem-solving methods. You may well say that knowledge of fact is basic to the other desired outcomes. You are correct if you define knowledge of fact to be more than the ability to repeat.

3. Students are not always placed in classes taught by teachers of their choice. The teacher and student come together as a result of the profession the student selected.

4. A tacit and false assumption often made is that the student knows why he is taking the course, what its purposes are, how the subject fits with other subjects, how and where the content of the course may be applied, and how to study the course content in order to earn a satisfactory grade.

5. The essential elements of a learning situation are: a living organism with the capacity for incentives that can lead to motives, an environment that is stimulating to the organism, and a temporary inability of the learner to satisfactorily respond so that he may gain the incentive. It is assumed that motives develop from within. It is the inner state of need of the learner that is necessary if the learner is to engage in purposeful learning. You may use the terms needs, wants, interests, etc. to describe these motivating conditions.

6. You are guiding the learning of students outside the classroom as well as inside. You are affecting students by virtue of your position on a faculty even though you are not in direct contact with a particular student.

Teaching and Human relationships

Teaching is essentially a problem in human relationships which involves the dynamic interaction of human personalities, the central personalities being those of the teacher and students. Insight into the nature of teaching and its improvement may ensue from a more thorough understanding of these human relationships.

Students have been thought of as groups for many years. You speak of a good class, an average class, or a poor class. You know, of course, that a classroom of pupils is more than a mere aggregation of individuals.

Actions are determined by objectives

The direction and guidance of learning is one of the major tasks a teacher faces. He directs learning by determining the types of experiences students have. A teacher can never deliver the end product directly to the learner.

Motives

One part of the task of the teacher is to help students develop motives, the development of that inner drive or the release of energy needed for learning. It must be remembered that the motives involve the whole personality of individuals. It is true that some motives involve few and some many aspects. Your students in chemistry or pharmacy are present in classes as a result of a composite of motives not just the love of pharmacy or chemistry. In fact, they may really not like either one and still be there.

What kinds of teachers' actions may produce the desired motives? Teachers must help students define their goals. A problem in the study of valence is more readily studied and solved if the learner knows what he is trying to do. Have you had students in you class ask the question, "Why are we studying this?" or make a statement such as "I think I might see this if you could help me see where this leads us or where it fits." These are not stated idly. They indicate a need on the part of the student. The teacher must note this and act accordingly. Care must be exercised not to project a goal that is too remote.

The definition of a goal in a laboratory activity may involve the understanding of the problem to be solved. The definition of a goal in the study of organic chemistry to the pharmacy student may involve seeing the place of organic chemistry in the practice of pharmacy.

It is known that rewards are effective in learning. These rewards are often success in performing a task. A teacher may also compliment a student upon his successful completion of a task. If the teacher is to make use of this principle, he will not make the success impossible. This is often done in the preparation of examination questions or in the preparation of assignments. Examination questions stated as "Discuss the influence of the AACP on the practice of pharmacy" give the student no goal and no possibility of success.

Studies do not support the opinion that students are stimulated to do better work by making the task difficult. In fact, this practice resulted in frustration and a decrease in achievement. The teachers job includes keeping a balance between the easy tasks and those that frustrate most of the group.

Teachers can help establish motives through the showing of films that orient the student to the problem at hand. They may involve the students in discussing the nature of the topic to be studied. They may perform demonstrations to point up the problem to be investigated. They may provide an overview of the area to be studied and also show how this fits into the total pattern.

If the teacher is concerned with motivation, he must develop, devise, or borrow materials and methods of instruction that are challenging and even exciting to the student.

Explanation

Although probably the most important facet of a teacher's job is that of motivation, he also has a responsibility for explanation. To many teachers this means giving a lecture. A lecture is fine for providing a common background for the pupil in your class; however, it fails more often in clarifying details. It is agreed that one does not discuss facts as he does opinions and that discussion in a class of 100 is nearly impossible. It is not agreed, however, that the teacher cannot pay attention to explanations in a large class. Class lectures if used must be concerned with explanation and not just presentation. Covering ground is not teaching.

You may well ask, "How can I determine where explanations are necessary?" You could give a pretest . You could ask students a few questions, even in a class of 100. You should suspect, as a result of your experience where the difficulties may exist.

How about the teaching procedure if you are presenting a new fact or idea? Ask yourself these questions: 1. Can this be demonstrated? 2. Is the demonstration large enough to be seen by all students in class? 3. How can I make the student aware of the problem to be investigated and the observations to be made? 4. Does the pupil have the necessary academic background to make these observations and study this problem?

When these are all answered to your satisfaction, you begin the planning of the lesson. Try to practice a good basic principle in teaching. In order for a student to understand the explanation of a fact he must be aware of the existence of the fact itself. First we establish the existence of a fact and then we explain it. With the fact established the student can react to the explanation and even ask some questions. Do you know that more often than not the negative response to your question, "Do you have any questions on this?" occurs because the student does not know enough to ask a question rather than his understanding of the principle involved.

A Method of Attack

How much time is spent in college classes on, "How can we solve a problem?" Very little in science classes, yet the most highly prized methods of solving problems are called scientific methods.

The teachers' actions here must be one of aiding students in the analysis of a problem. This cannot be a lecture. Yes, we all agree that to solve problems you

need facts, but, the possession of facts does not guarantee the ability to solve problems. This is taught in small groups or individually. You learn to analyze problems by analyzing problems and not be watching others analyze them. The teacher's part is one of direct or indirect questioning. The questions are to be of general nature but are to direct the student's attention to the employment of a process.

By involving students in discussion, analysis of problems, and formulation of conclusions, you increase the retention of materials learned. You are employing the principle of varied repetition. It should be possible for the teacher to have students repeat the facts needed so that all may benefit.

Teacher student relationships

You now have before you a brief picture of the teacher and the student in the classroom. As teachers we have very little influence over who enrolls in our classes save for a few perfunctory screens so we must be most concerned about how we can best do our jobs. We must consider schools as people interacting.

Certainly we must consider the importance of the curriculum, the methods of instruction, the administrative organization, etc. These, however, are only the vehicles or instruments, the effectiveness of which depend upon the human being involved.

In any discussion of student-teacher relationships we must take cognizance of the total relationship and the purposes for which these relationships were established. Since teachers' purposes are educational, our concern should be with the teaching-learning relationships.

It has been stated that the school is only one social institution transmitting culture to youth. Our purpose in schools is to transmit the culture to members of oncoming generations in such a manner that they will become sufficiently independent as adults to develop their own potentialities.

As we observe teacher-student groups we are able to identify the general reactions of students to teachers as: warm, friendly, personalized give and take, the teacher accepted as a group member, apathetic indifference, active negativism, open hostility, or fear.

A pertinent question emerges, "What determines the status of the teacher in a group?" There are factors as, enthusiasm, scholarship, like or dislike, interests, teaching skill, modesty or arrogance, human, fair, sarcastic, shy, social adjustment, respect for people, partial, etc.

It is interesting to note that individual classes soon after their first meeting form a social group. With this comes a routine, a set of expectations, and interpersonal adjustments.

It seems that the teacher must be aware of the role assigned him by the group. Is he our leader, dictator, fountain of knowledge, security giver, master, dispenser of skills, enemy, friend, etc. If the role, as seen by the teacher, is in conflict with that seen by the students difficulty and conflict will result.

When students see the teacher as an enemy, this calls for war. He is one to be fought or at least outwitted at every opportunity. There may even be open campaigns aimed toward defeating the teacher.

This type of situation emerges from teachers being unreasonable in their demands, arrogant and self-centered in their actions, sarcastic in their remarks, unfair in their marking and/or crude in their relations with individuals.

The students may see the teacher as an automat or pinball machine. If you know how, when, or are lucky in pulling the right lever, you will have delivered to you the desired knowledge. These teachers seem to care very little for the students, but if properly stimulated will teach a good class. Maybe he is more interested in research or writing, than in teaching. Maybe he knows that his salary raise or promotion depends upon the number of pounds of published material he accumulates. Teachers too have motives.

Some teachers are the dispensers of knowledge. These may care very little for students and even less for teaching but they are conscientious in carrying out an assigned task. These teachers are confusing to students. The comment is often made, "Old ________ may not be so hot in many ways but he sure gets you by the state boards."

The security giver is able to transmit faith in him to the group. He has the ability to meet a group and help them see their needs and to develop interests. He may, however, not help the students to become independent.

Another role seen is that of "one of the boys." This person loses his position as a teacher very quickly.

There are teachers who are trusted friends to most students. What role a teacher gains depends upon his actions.

Popular opinion suggests that a teacher, to be effective, must like his students and the students must like the teacher. Studies seem to show that the teacher does not have to like the students and the students do not have to like the teacher. Although mutual liking is not indispensible, studies seem to indicate that the teachers pupils like most are the most competent.

Does this personal liking of the pupil for the teacher mean that the teachers should consciously strive to cultivate the personal liking of students? It seems that a word of caution must be sounded. Since a teacher's professional aim is the welfare and development of the pupils under his care, his personal relationships with them must be directed and controlled.

Teachers do tend to want students to like them and students want teachers to like them. Teachers also seem to agree that at least there should be an absence of dislike among those who work together and so far as possible a personal liking. This in no way intimates personal entanglements with students. Personal or affectional entanglements often destroy the objectivity that is essential to insight into a pupil's behavior. It may also make him the subject of retaliatory action. The type of action based upon "How can he do this to me after all I have done for him?"

Inasmuch as a harmonious and friendly feeling on the part of the student toward the teacher enables the student to develop more fully, the teacher should do what ever possible to reduce discord, conflict, and indifference provided he knows what he is doing and is first concerned with the welfare of the student.

There are some common factors that can be discussed relative to the teacher's personal characteristics that may help make the previous statements more meaningful.

1. Remember that you are not a know it all. Your ignorance varies in depth from subject to subject and topic to topic. This is also true of your students.

2. Your students are persons not things. Persons are afforded certain freedoms and dignity.

3. When you come before a class you are not representing yourself. You are representing a concern of the intellect, a subject discipline. We will grant that every professor expounds subject matter he does not understand; however, care must be taken not to kill the concern of many intellects for the subject through our inadequate treatment of the subject itself. Students often associate subjects with teachers. It is important that this interest in subjects be nutured by all means.

4. Good teachers have some traits in common.

   a. They know their students.
   b. They know their subject.
   c. They are exciting to others.
   d. They are intensely human, and
   e. They are thoroughly mature.

   Poor teachers also have some common traits.

   a. They are sarcastic.
   b. They have fixed ideas so new ones never come.
   c. They are shy and insecure.
   d. They show favoritism.
   e. They do not know their students.
   f. They take out their maladjustments on students, and
   g. They considered students as an ever-present nuisance.

5. It seems that every teacher should:

   a. be aware of his current assignment
   b. examine his role in this assignment in terms of his goals and the goals of the class, and
   c. take steps to change the assignment if it seems inadequate.

Summary

It seems that interpersonal relationships are as fundamental in motivational patterns as are specific teaching devices. The older conception of teaching and of learning as a sort of fueling process with knowledge passing from one tank to another has been replaced by emphasizing the dynamics of interpersonal and group action during learning. An individual student is motivated to learn because he is the sort of person he is, surrounded by the sort of teacher and peers he has in his immediate environment and by the other physical and social forces that make up his environment. Motives are not simply explained. You may be teaching the preparation of aromatic waters and the pupils are learning how boring the practice of pharmacy must be. A personal reaction may cast a shadow over the overt method of instruction you employ.

A capable teacher is alert to signs of bad motivation and low morale. Listlessness, aggressive behavior, inattention, attitude that the content is unimportant, and unwillingness to attempt a task are common signs of poor motivation. These may demand some teacher reorganization both personally and professionally. We are the expert salesmen of culture. Our sales approach must be fitted to the nature of the product and to the personal characteristics of the potential purchaser.

DISCUSSION

Dr. Wilson wondered if a discussion of the (learning process) with students at the beginning of the class would lead them to an appreciation of the problem.

Dr. Pella doubted that freshmen and sophomore students are sufficiently mature for this. If, however, students be advised in advance of the teaching plan, they will be prepared for accepting the discussion of various topics at the proper time.

Dr. Wilson: "Would it be advisable to try to tell the student your problem as a teacher?"

Dr. Pella agreed that it would be advisable if it were done very carefully without giving the impression that you are providing an excuse for yourself.

A comment on the display of temper by the teacher prompted Dr. Pella to suggest that good teachers may do this as part of an act, and that students are able to recognize the teacher's behavior as an act.

Dr. Stuart raised the question of the students' responsibilities in the student-teacher relationship.

Dr. Pella agreed that students do have a responsibility but not as great as the teacher's.

The further discussion brought out the fact that changes in student attitudes may depend on their appraisal of the teacher as a new man requiring initiation or as the kind of teacher who has proved himself acceptable to them.

Dr. Webster asked for comments on the situation where dishonesty becomes a problem with an entire class.

Dr. Pella recommended a discussion of the situation with the class, conducted in a way calculated to avoid unfavorable publicity. The teacher must demonstrate his awareness of the situation and be in position to support it with facts.

Dr. Feldman inquired about means for developing leaders in the class who would benefit the learning process.

Dr. Pella pointed out that class morale depends on the relationships which exist within the social group, such as a class of students. It is difficult to say just how the leadership can be pointed in the right direction.

Dr. Cole wondered how superior students could be properly encouraged without eliciting a charge of favoritism.

Dr. Pella expressed the thought that the gifted student does not want attention that sets him apart. Such a student can be encouraged without any exchange of confidences. He will accept responsibility in a mature way. His fellow classmates will recognize his ability and, if he be a good colleague, they will respect him and will be glad to see him get ahead. The teacher should not exchange confidences with him, nor become entangled in any way beyond the professional level.

Wednesday Session

Frank E. Di Gangi

Chairman

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SYLLABI OF COURSES IN DRUG ANALYSIS

Lee F. Worrell

I'm afraid that I have taken considerable liberty with the assigned topic--especially with the word "Syllabi"--in the title; but fortunately Dean Hager, in his letter inviting me to participate in the program, gave me quite a bit of leeway as to what I should talk about and I wish to express to him and to the other members of his committee my appreciation for the opportunity to discuss with this group the subject of chemical and pharmaceutical analysis courses in the undergraduate pharmacy curriculum. In 1952 at Ann Arbor, when the program of the Seminar was last devoted exclusively to the area of pharmaceutical chemistry, I was asked to discuss the graduate program in analytical pharmaceutical chemistry.

In that talk I alluded briefly to the undergraduate work in this area in the following words:

"I believe that every college of pharmacy should offer undergraduate work in pharmaceutical analysis of sufficient scope to provide all pharmacy college graduates with a realization of the importance of the control of the quality of medicinals to the practice of their profession. Furthermore, I believe that undergraduate courses in drug assaying offer an excellent opportunity to inculcate the principles of reasoning and logical analytical thinking as well as to offer, in the laboratory, increased opportunity for practice in precise weighing and measuring. I, therefore, think that at least three or four credit hours of drug assaying in addition to elementary quantitative analysis should be a required part of the undergraduate curriculum in pharmacy."

At that time the topic was such that it was not appropriate for me to attempt to explain these beliefs in relation to the needs of pharmacy graduates who were not going into graduate study. Now, the present assignment, if I understand it correctly, is to examine with you the values of courses in chemical and drug analysis to the pharmacy graduates who are to become retail pharmacists, hospital pharmacists, medical service representatives, and other professional pharmacy practitioners after they have terminated their formal education at the level of the bachelor's degree. It is hoped that this examination will elucidate these values, will consider how they may best be made available to the student, and will stimulate us as teachers of these courses to re-evaluate our course material and presentation with due consideration to the actual needs of this group which constitutes by far the majority of our students.

In order to re-acquaint myself with what others had had to say about undergraduate analytical courses in the pharmacy curriculum, I turned to the American Journal of Pharmaceutical Education. Incidentally, the cumulative index for the first thirteen volumes was helpful here. In the twenty-one volumes published since the Journal originated in 1937, I found only thirteen papers which were at all pertinent to the topic. These are listed with the other references and will be referred

to and quoted from a little later. Since most of these papers had been presented at meetings of the Teachers' of Chemistry Section of the AACP, I suspect that they should not be classified as spontaneous contributions to the literature.

I also reviewed the material on analytical courses contained in the five editions of the Pharmaceutical Syllabus, 1910 to 1945, the material in the so-called Charter's Report (Basic Material for a Pharmaceutical Curriculum 1927), the pertinent papers in the Proceedings of the 1952 Teachers' Seminar on Pharmaceutical Chemistry, and Blauch and Webster's The Pharmaceutical Curriculum (1952).

One result of the study of this material was that I gained the distinct impression that during the first three decades of cooperative curriculum planning (1910-1940), the importance of analytical work to the pharmacy student was so firmly and uniformly accepted that very few felt it necessary to discuss it in print. The following figures showing the minimum number of clock hours allocated to quantitative analysis and drug assay in the various editions of the Pharmaceutical Syllabus contribute to this impression.

1910 Edition (2-year course of 1000 hours)	
Quantitative Analysis	50 hours
Drug Assaying	50 hours
1913 Edition (2-year course of 1200 hours)	
Quantitative Analysis	50 hours
Drug Assaying	50 hours
1922 Edition (2-year course of 1200 hours)	
Quantitative Analysis	50 hours
Drug Assaying	50 hours
(additional year of 750 hours)	
Analytical Chemistry	300 hours
1932 Edition (4-year course of 3000 hour s)	
Quantitative Analysis	96 hours
Pharmaceutical Analysis	112 hours
1945 Edition, tentative (4-year course of 3168 hours)	
Quantitative Analysis	160 hours

It was not until the pressure for time within the four year course became extremely great that we observe the attempt to decrease the time allocation for analytical work and to combine the two previously recognize courses into one. It should be noted that the course referred to in the 1945 Edition as "Quantitative Analysis" was actually described as a combination of elementary quantitive analysis and drug analysis. Furthermore, in the opinion of the speaker, it would have been utterly impossible to present the course as described within the allotted time.

In 1927 the authors of Basic Material for a Pharmaceutical Curriculum first described the type of pharmacist for which they were attempting to outline a curriculum. He should be represented they say "by the proprietor of the neighborhood drug store in the city and of the pharmacy in the small towns throughout the country." They emphasize that they are not referring to specialists for whom specialized courses should be developed. Then they say that it is one of the duties of this pharmacist "to be competent to read the USP and the NF." In the section of the

book devoted to chemistry, the authors make it quite clear that they consider that competency to read these compendia involves the ability to understand and solve all chemical problems derivable from them and to perform the tests and assays, physical and chemical, which are found therein. The authors apparently did not feel that it was necessary to explain why this retail pharmacist needed these abilities. They simply stated, if I may paraphrase slightly, that the pharmacist is a professional man and that therefore he must know not only how the activities of his profession are performed but also must have mastered the principles and fundamental facts upon which the methods are based.

Studying the literature from roughly 1940 to the present, however, created quite a different impression. Thus, in 1939 we find James discussing the objectives of quantitative analysis in the pharmaceutical curriculum. In 1940 DeKay presents the advantages of teaching qualitative and quantitative analysis in a school of pharmacy rather than in the department of chemistry; and Webster defends flexibility in that part of the curriculum devoted to pharmaceutical chemistry. In 1941 Jannke, in an article particularly pertinent to our discussion today, outlines the value of analytical chemistry to the pharmacist; and both DeKay and Parks separately consider the question "Should Separate Courses Be Offered in Drug Assay and Quantitative Analysis?" Both answered the question in the affirmative. The topics discussed in the above-mentioned papers create a vague suspicion that the need for analysis courses is during this period not quite so unanimously acknowledged, and that suggestions concerning consolidation and possibly diminished time allotments may have been made. In other words various questions seem to have been raised and some teachers have attempted to answer them. The recommendations of the 1945 Syllabus would seem to indicate that possibly the questions and the suggestions had had some effect, at least temporarily.

In 1954, in spite of or perhaps as a result of, the publication of The Pharmaceutical Curriculum by Blauch and Webster in 1952, we find the Teachers' of Chemistry Section holding a symposium on "The Fate of Quantitative Analysis and Pharmaceutical Assay." In introducing the speakers constituting the forum, C. E. Miller formulated some questions which probably typify the ones mentioned above and which he at least believed were being asked in one form or another of professors in charge of analytical courses. A few of these questions are quoted:

"Why should the retail pharmacist be required to take coursework which obviously he will never use in the future?"

"Are you going to make control chemists of all of our students?"

"Is it not possible for the pharmacist of today to carry out his professional requirements without a knowledge of quantitative pharmaceutical chemistry?"

Following this challenging introduction Purdum talked on the importance of drug assay courses to pharmacists in retail and hospital practice; Johnson on their importance to pharmacists in industry; James discussed general objectives for quantitative analysis and drug assay and outlined the scope of these courses; and the present speaker discussed prerequisites, time allotments, methods of presentation, and sequential arrangement of the analytical courses.

Finally in 1955 Sprowls presented a paper on "The Dispensing Pharmacist's Need for Training in Chemistry" in which he spoke of the need for analytical training as well as that for the other chemistry disciplines.

Thus most of the literature from about 1940 to date is explanatory and sometimes almost defensive in character. That this is not entirely true is exemplified by a paper by Green in 1951 which straightforwardly attacks the problem of how to evaluate laboratory results in quantitative analysis and by a paper in press by Gearien which presents a new and very interesting approach to the drug assay course.

I would like to mention one other impression which a study of the papers of the last two decades created. With the notable exceptions of the papers by Jannke, Sprowls, and to some extent Purdum, the justification--and I use this word advisedly--for undergraduate drug assay courses is based too heavily on the fact that some students change their plans, either shortly before or after graduation, and instead of becoming retail pharmacists go into graduate study, hospital practice, the pharmaceutical industry, or into other pursuits for which their analytical training is extremely important. We all know that this happens; and I expect that we all agree that the basic curriculum in pharmacy should be such that those students who do change their vocational objective should not be unduly handicapped. Of course if the change comes early enough, these students should take further elective work in pharmaceutical analysis; but this is not always possible.

The abovementioned argument could be and is used for all the various areas within the pharmacy curriculum. The pharmacy graduate, even though he has not selected the proper electives, should have acquired the fundamentals of each sufficiently well so that he has as much vocational freedom as possible after graduation. No teacher would argue against this principle; but I believe we must today look beyond these fringe benefits of pharmaceutical analysis and squarely face the questions "What values do quantitative analysis and drug assay have for the student who does go into retail pharmacy (and most of them do)?" and "Can we conscientiously allow a student to become a pharmacist without at least having attempted to impart these values?"

I hope that in the discussion following this paper some opinions relating to these questions will be voiced. At the close, borrowing freely from several of the above-mentioned authors, I have attempted to point out at least some of these values.

Now I would like to discuss rather briefly the necessary prerequisites, the position in the curriculum, and to some extent the content of a course in drug analysis which would be a required course for all pharmacy students, it being understood that nonretail people would elect further work in the field. Much of this material has been previously outlined in the literature in considerable detail with a remarkable degree of agreement at least among drug assay teachers.

The prerequisites in chemistry should include general chemistry, qualitative analysis, quantitative analysis, and elementary organic chemistry as the minimum. The general and qualitative may well be combined in a two-semester course. Such

courses are standard offerings by many chemistry departments now and usually carry ten hours' credit. This would be followed by a year of organic chemistry and one semester of quantitative analysis. In my opinion, it doesn't make much difference whether the latter is taught by a pharmaceutical chemist using inorganic drugs as laboratory examples or taught by the chemistry department. The important thing is that the fundamental principles of analytical chemistry be thoroughly instilled. Parks more than fifteen years ago stated "The chief dangers in teaching quantitative analysis and drug assay in a combined course lies in the fact that the fundamental principles of quantitative analysis are likely to be slighted in order to emphasize the application of such principles to pharmaceutical analysis." If a choice were available, I would prefer that the chemistry department teach this course; but if local conditions are such that it is more conveniently taught as pharmaceutical chemistry, it can be handled very satisfactorily in that manner. I would still like to see the course entitled "Quantitative Analysis" and taught as a strictly fundamental course with most of the applications deferred until the following course in drug analysis.

At Michigan for the past few years we have been able to arrange this sequence somewhat differently. The student takes eight semester hours of general chemistry in the first year, organic chemistry in the second year, and during the third year four semester hours of a course given by the chemistry department entitled "Introductory Analytical Chemistry." This is a combination of qualitative and quantitative analysis and serves very satisfactorily as a prerequisite for the required drug analysis course. The student is not quite as adept in the laboratory as one who has had the old four semester sequence of general chemistry, two semesters, qualitative and quantitative analysis, 1 semester each; but he compares very favorably with transfer students who have had a combined general and qualitative course followed by one semester of quantitative analysis. Students planning to do graduate work are advised against this shortened sequence, but it seems quite satisfactory for the retail option.

Other prerequisites for the drug analysis course should include mathematics and physics, pharmacy courses (including manufacturing if offered) up to the dispensing course, pharmacognosy, and preferably physical chemistry, biochemistry, and at least inorganic pharmaceutical chemistry if these courses are required in the curriculum.

If it is to achieve its purpose, the drug analysis course should be a senior level course in the last year of any curriculum except possibly a six-year sequence. Quantitative analysis can come earlier and meet the demands of the physical pharmacy people for an analytical prerequisite. This is one of the things that cannot be accomplished by a one-year continuous pharmaceutical analysis sequence including quantitative analysis, and is one good reason for giving quantitative analysis and drug analysis as separate and distinct entities.

I do not propose to suggest an outline of the specific contents of the required course in drug analysis. There is a wide range of type processes available in the tests and assays of the USP and NF and a profusion of typical unofficial methods in the periodical literature and in such books as Methods of Analysis of the AOAC.

Parks and James, in papers previously mentioned, have both given comprehensive lists of procedures from which a selection may be made. Variability in the actual type procedures used as examples in the course as taught in different schools and by different teachers is to be expected and encouraged. The content of other courses in the curriculum and the individuality of the instructor will contribute to this. Obviously if laboratory exercises in the quantitative analysis course have consisted of assays of official inorganic drugs, duplication of these is to be avoided. Even if such is not the case, there is probably need for very little repetition of the simpler volumetric and gravimetric methods for the inorganic drugs. Gearien recognized this in a recent paper in which he stated "It is logical to stress the analysis of organic compounds in Drug Assay." His outline of a course based on the more common functional group methods of organic analysis presents a new approach to the problem of organization of material in the drug analysis course and deserves serious study, although not necessarily direct imitation, by other teachers in the field.

At Michigan we use the official assay for Sulfur Ointment as the beginning laboratory experiment. This enables us to stress the fact that in pharmaceutical analysis, particularly in the analysis of pharmaceutical preparations, the problems of separation are frequently the paramount ones, and that the final determination is apt to be in many cases an utilization of procedures already familiar to the student. In this case the final determination of sulfate ion, and hence of sulfur, by precipitation with barium serves as an example through which in the didactic portion of the course it is possible to correlate the official gravimetric procedures with the fundamentals of gravimetric analysis previously learned in quantitative chemistry. This experiment is followed by the official assay for Camphor Spirit which is gravimetric in type but involves an organic reaction. Here we are able to emphasize that the same fundamental principles apply in organic reactions and that methods of calculation previously learned are equally applicable. Using some samples with an appreciably greater camphor content than the official spirit enables us to introduce the subject of proper preservation of pharmaceuticals with such a simple example as solvent evaporation. It also points out the necessity of modifying amounts of sample or reagent used when deteriorated samples are encountered. Both of these ideas are of course re-illustrated with more complex examples as the course proceeds; the point here is that they are introduced early in the course and continually re-emphasized.

Other laboratory exercises performed include determination of glucose by polarimetry and by copper oxide precipitation, alcohol by specific gravity and by use of the immersion refractometer, nitrogen by Kjeldahl, aspirin in tablets, phenol, saponification and iodine values, index of refraction of oils using the Abbé refractometer, a colorimetric determination, and simple volumetric and gravimetric alkaloidal determinations. This is not the complete list and I'm certainly not advocating it as an ideal one. However, each experiment has been chosen with a definite purpose in mind and is used as a starting point for illustrative discussion in the classroom.

Different teachers would undoubtedly choose different laboratory exercises and material for didactic instruction. The objectives outlined by Blauch and Webster for the drug assay course provide an excellent guidance for this selection and should be

used to evaluate the relative desirability of tentatively selected material.

Now to come back to a question which we left unanswered earlier: "What values does the drug analysis course provide for the majority of our pharmacy students?"

Although the course is not intended or expected to produce expert analysts, the knowledge of a wide variety of analytical procedures and of the problems of quantitative separations which the student acquires should give him an appreciation of and respect for modern methods employed to maintain the standards of identity, quality, and purity of medicinal substances and preparations. He should gain a firm realization of the legal status of the USP and NF and of their great importance to public health by virtue of their establishment and maintenance of drug standards. This background knowledge should contribute to his professional status and enhance his justifiable pride in his profession.

By stimulating students to apply scientific principles to pharmaceutical problems, Gearien says that the course should "develop in the student the proper scientific approach." James is discussing the same value when he refers to the capacity to understand, interpret, and use the fundamental principles. He also mentions the development of ability to read and interpret the literature of the profession and to formulate clear, concise, and complete reports. The development of critical judgment with a realization of the importance of controllable and inherent errors and an honest appreciation of and the continuing desire to achieve accuracy and precision are mentioned by several authors.

Purdum points out that the student becomes aware of quality in drugs and chemicals and learns the differences between technical, medicinal, and analytical grades, which is of direct economic importance to him in his purchases of prescription and other chemicals. He and many others note that drug assay courses serve well to emphasize and illustrate instability in preparations and the reasons for the necessity of correct storage precautions.

The improvement in weighing, measuring, and filtering techniques gained in drug analysis is of direct value in compounding and dispensing. Although it may be that the modern retail pharmacist does little compounding, the potency of many modern drugs makes close attention and superior technique mandatory in those instances in which compounding is necessary.

Few of the values mentioned are to be gained solely in the drug analysis course; they should be stressed throughout the entire curriculum. Nevertheless, a well-planned and well-presented course in drug analysis, coming near the close of the student's formal education, serves admirably to emphasize all these values and is perhaps the best way in which a great many of them may be imparted.

I would like to close with a quotation from a commencement address given by Dr. Robert D. Swanson, president of Alma College, a few weeks ago. Of course he was speaking in general terms and as far as I know has no pharmaceutical connections whatsoever, but this is what he said. I think it is quite apropos of our discussion this morning.

"It is education's role to instill the quality of discrimination, the capacity to think critically and responsibly, the ability to choose between that which is worthy and that which is unworthy, between that which is real and that which is phony."

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DISCUSSION

Dr. Feldman emphasized the need for more instruction on the qualitative aspects of drug analysis, especially in regard to drugs that are organic in nature. The advantages of presenting this material concurrently with the dispensing course were mentioned. Certain topics which were suggested by the speaker are presented in other courses.

Dr. Worrell agreed that qualitative tests for identity and purity, particularly in the case of organic drugs, should be presented. Density measurements are required in determinations of alcohol content of drug products. The course content must depend on the syllabi of other courses in the curriculum, and on cooperation among the teachers of the various courses.

Dr. Osol described an elective drug assay course following the basic course in quantitative analysis. The elective course, which probably would be required in the five year curriculum, stressed the instrumental methods of analysis.

Dr. Worrell indicated that the amount of time allotted to the required drug analysis course made it necessary to defer some of the special instrumental methods to an elective course of interest to students who are contemplating graduate study or industrial pharmacy.

Dr. Schwartz pointed out that students are reluctant to elect a laboratory course and wondered if the course should be required.

Dr. Worrell reiterated that drug analysis should be a required course although its content may vary in different schools.

Dr. Mitchner suggested the need for instruction in microbiological methods for control of vitamins, antibiotics, etc.

Dr. Worrell agreed that both microbiological and pharmacological control procedures warrant consideration, but that usual limitation of the teacher and facilities would present difficulties.

Dr. Small endorsed Dr. Feldman's views and pointed out that the qualitative organic procedures are covered in his organic medicinal products course.

Dr. DiGangi stressed the importance of offering quantitative drug analysis in the third year of the five-year curriculum in preparation for the capstone courses of the curriculum and for a senior elective drug analysis course involving special analytical methods.

COURSES INVOLVING PHYSICAL CHEMICAL ASPECTS OF MEDICINAL AGENTS AND DOSAGE FORMS

Alfred N. Martin and Marvin J. Chertkoff

The trend today in college education is toward the teaching of principles and methods with the realization that they are equally as important as facts and techniques. However, before the student can learn the fundamental principles and apply them to the solution of problems, he must acquire a minimum body of facts. The beginning courses in basic science, mathematics and pharmacy provide this information together with a qualitative view of the broad principles and laws that undergird the various areas of knowledge.

Later courses then consolidate the sometimes disconnected pieces of information, and the upper level courses should finally correlate the principles and facts in a quantitative way and apply them to the solution of practical problems. As an outgrowth of this trend, increasing emphasis is now being centered on physical chemical principles in the pharmacy curriculum, and separate courses in mathematics and physical pharmacy are being introduced at an intermediate and advanced level.

Recent Curriculum Changes In Related Fields

Recent reevaluations of objectives and changes of curricula in some of the basic and applied sciences parallel the present upheaval in pharmacy education. Some of the alterations that are being effected in chemistry and chemical engineering are outlined here before changes in the pharmacy curriculum are discussed.

In the various plans for improving the undergraduate chemistry curriculum, reported in the 1958 April and May issues of the Journal of Chemical Education, emphasis was placed on atomic and molecular structure and the newer concepts of the chemical bond with a definite departure in some schools from the classical sequence of general and inorganic, analytical, organic and physical chemistry. Many of the innovations are patterned after Brown University's chemistry curriculum (J. Chem. Ed. 26, 10, 1949) and the new approach is illustrated in the book, Chemistry of the Covalent Bond, by L. B. Clapp, published by W. H. Freeman, San Francisco, 1957.

Less radical departures from the curriculum of the past are represented by the programs at Penn State University and the Massachusetts Institute of Technology. Penn State divides the curriculum into two options, one for chemistry majors going into chemical industry, government and research and a second plan for those desiring a liberal education with emphasis on chemistry. M. I. T. has strengthened and revitalized its chemistry courses with more fundamental material but has held to the classical course sequence.

Since its beginning, chemical engineering was divided for teaching purposes into courses entitled unit operations and unit processes. Unit operations considers the basic physical elements of such topics as flow, distillation, crystallization, whereas unit processes is concerned with the chemical processes such as sulfonation, hydrogenation, esterification. Until recently this division into unit operations and unit processes proved to be adequate in the educational scheme of the chemical engineer. However, since the advent of biochemical engineering, nuclear engineering, the chemistry of rocket fuels and similar modern advances, the chemical engineer has found it increasingly difficult to cope with the problems arising in these technologies in terms of classical unit operations and unit processes. At the 1952 symposium in chemical engineering science (Chem. Eng. Progress 48, 323, 1952) the conclusion was reached that tomorrow's engineer must learn the fundamental principles underlying unit operation and unit processes rather than the technical details of these subjects.

With the changes that are now being made in the chemistry and chemical engineering curricula, it is felt by many that the students will learn considerably more basic material and the courses will possess sufficient flexibility and adaptability so as not to require considerable relearning by practicing chemists and engineers and a complete overhauling of courses each time new technologies, such as those now developing from nuclear and rocket research, arise in the constantly changing pattern of science.

Newer Concepts In Pharmaceutical Science

Pharmacy, too, is rapidly becoming a highly specialized science as well as being a profession, and accordingly is applying a number of basic scientific principles to suit its own needs. Some of these newer pharmaceutical concepts which should be taught in the pharmacy curriculum include:

1. The applications of thermodynamics and chemical kinetics to the study of drug decomposition.

2. Newer accelerated testing methods for estimating shelf lives and expiration dates of marketed drug products.

3. The application of reaction rate theory to drug absorption, distribution and elimination from the body.

4. The development of time disintegration and sustained release medication based on a knowledge of the physical chemical properties of drug molecules and their vehicles.

5. The combination of drugs into molecular addition compounds for the purpose of controlling onset and duration of action in the body and retarding the rate of breakdown.

6. The application of new principles of dissolution, solubilization and emulsification in the formulation of acceptable dosage forms.

7. The application of interfacial phenomena, particle size analysis, and rheological methods in the development of new dosage forms and in the modification and control of drug action.

The pharmacy student of today is the practicing pharmacist of 25 years hence, and we must organize the current curriculum in terms of what the pharmacist will be reading, discussing and applying not only in the immediate future but at the peak of his professional career. Obviously we cannot predict the specific drugs, dosage forms and modes of drug action which will be important in the future, but we can practice teaching methods which will develop in the student the ingenuity to acquire new knowledge, to analyze it critically, and to make sound judgments based on fundamental principles in the years ahead.

Too often our students spend their undergraduate years memorizing disorganized facts, never reaching the desired stage where these are brought together into an integrated body of concepts and methods. Admittedly we must make our students aware of the factual knowledge which is constantly accumulating in pharmacy, but it is equally important to correlate these facts for the students by elucidating the principles on which they are based and pointing out the applications to which they can be put.

The teacher discharges his duties well when he discusses fundamental concepts, clarifies difficult ideas, and presents selected facts to illustrate broader points of view. Too often the pharmacy teacher assumes the role of gasoline attendant, filling the student to the mark with drug names, formulas, doses and uses, and sending him out on the professional highway with a full tank of knowledge. Frequently this type of fuel is soon burned up and forgotten.

The new curriculum should include courses that stress drug classes and chemical and pharmacologic relationships among the drugs within each class, rather than requiring rote memorization of synonyms, organic formulas, trade names, and other factual information regarding a large number of individual products. In pharmacy and pharmaceutical chemistry, the classroom and laboratory work should emphasize the chemical kinetics of drug decomposition and the use of buffers, antioxidants and complexing agents for the stabilization of pharmaceutical products. In pharmacology and medicinal chemistry, discussion should center around drug action in terms of structural properties, steric, polar and resonance effects, and the relationships of these to physiological changes.

Proposed Undergraduate Courses In Physical Chemical Principles

In 1952 Blauch and Webster recommended calculus and statistics and a 6-credit course in physical chemistry as prerequisites to physical pharmacy, and at the same time they presented objectives and course outlines for these subjects. Since that time various proposals have been made for introducing physical chemistry and physical pharmacy either separately or in an integrated form into the pharmaceutical curriculum. These modifications were outlined in a previous paper on physical pharmacy presented before the Section of Teachers of Chemistry of the American Association of Colleges of Pharmacy in Los Angeles, May 1958.

It was observed at that time that while some schools may be able to develop a sequence of courses along the lines proposed in The Pharmaceutical Curriculum, others will be faced for the present with teaching physical pharmacy without the desired prerequisites. Nevertheless in an integrated two-semester course of 6 or 8 semester hours, it should be possible to include some introductory calculus, selected topics in physical chemistry, and pharmaceutical applications based on these principles. Such a course might be called physical pharmacy or physical chemistry in pharmacy and it could be taught by a physical chemist in the pharmacy school or a pharmacy teacher with adequate background in physical chemistry. The course in physical pharmacy may be accompanied by laboratory work; however, where the student also takes a physical chemistry and/or instrumental analysis course with laboratory, additional exercises in physical pharmacy may not be needed.

A typical undergraduate syllabus involving physical chemical aspects of medicinal agents and dosage forms is divided here for the convenience of discussion into two proposed courses; one involving 6 credits on fundamental physical chemical principles and a second of 3 credits on the physical aspects of medicinal chemistry. Brief outlines of courses in these subjects follow, together with examples of how these concepts can be presented to undergraduate pharmacy students.

The first course is designed primarily for third, fourth, or fifth year students, the second is a more advanced elective course for fifth year students. Prerequisites include basic courses in physics, quantitative analysis, and organic chemistry. Calculus is highly desirable, but if not available as a prerequisite, a certain amount of it can be incorporated in the course.

Outline of a Proposed 6 Credit Course Dealing with Elementary Physical Chemical Principles in Pharmacy

1. Fundamental Principles.

   Concepts and methods of science, dimensions and units, elementary mathematics review, introductory statistical methods and analysis of errors.

2. Structure and Properties of Matter.

   Elementary particles, atomic structure, the chemical bond, properties of matter, intermolecular forces.

3. Energy and the States of Matter.

   The gaseous state, heat and work, the liquid state, solids and the crystalline state, thermodynamics of phase transitions, x-ray and electron diffraction studies of crystals and liquids.

4. Solutions.

   Definitions, concentration expressions and calculations, additive, constitutive and colligative properties of solutions, ideal and real solutions.

5. Solutions of Electrolytes.

   Arrhenius theory, modern theories of strong electrolytes, colligative properties of solutions of electrolytes, Brönsted-Lowry theory, Lewis theory.

6. Ionic Equilibria.

   Acid-base equilibrium and the law of mass action, pH scales, hydrolytic equilibrium, activity coefficients, general acid-base equilibria in various solvents, relationship between structure and the strength of acids and bases.

7. Buffers and Isotonic Buffered Solutions.

   The buffer equation, buffer capacity, buffer systems in pharmacy and biology, colorimetric determination of pH, pH and buffer capacity of body fluids, methods of measuring tonicity, methods of adjusting tonicity.

8. Phase Equilibria: Solubility and Related Phenomena

   Solvent-solute interactions, solubility of gases, liquids, and solids, theories of the solubility of electrolytes and nonelectrolytes, the influence of temperature, solvent character and pH on solubility, the distribution of drugs between immiscible solvents, metal ion complexes and organic molecular complexes in solution.

9. Rate Processes.

   Chemical kinetics, decomposition and stabilization of pharmaceutical products, accelerated testing methods for predicting shelf life, kinetics of drug absorption, distribution and elimination.

10. Colloidal and Coarse Dispersions.

    Definition of terms, preparation and properties of colloids, stability of colloidal dispersions, surface tension, liquid and solid interfaces, surface active agents, micromeritics (particle size analysis), rheology (flow of disperse systems), emulsions, suspensions, gels.

11. Thermodynamics.

    The first law, thermochemistry and calorimetry, the second law and entropy, the third law, free energy, pharmaceutical applications.

Classical courses in the pharmaceutical chemistry of medicinal products have stressed source, synthesis, reactions, usage, and structure-activity relations. While some teachers have treated the subject from the standpoint of electronic structure and reaction mechanism, many have not found it possible to incorporate these aspects into the already overcrowded course dealing with the chemistry and pharmacy of medicinal agents.

An outline of a fifth year elective course involving 3 semester hours (48 hours of didactic instruction) and including a number of physical organic principles is presented here. The course would follow the medicinal products course and the basic course in physical chemical principles, and should be of particular interest

to those students contemplating graduate work. It should be taught by a pharmaceutical chemist or a physical pharmacy teacher with a good background in physical organic chemistry.

Outline of a Course in the Physical Aspects of Medicinal Chemistry

1. Review of Atomic Theory.

   Emphasis on electronic architecture.

2. Classes of Chemical Bonds

   Ionic, covalent, and coordinate covalent bonds, qualitative discussion of wave mechanical theory, sigma and pi bonds and their relationship to solubility, incompatibility and stability of drug products, secondary valance bonds and van der Waals forces.

3. Polarization Effects.

   Electronegativity and the inductive effect, tautomeric or resonance effect.

4. Reaction Rates.

   Review of chemical kinetics, absolute reaction rate theory, factors which affect rate (temperature, solvent and salts)

5. Reaction Mechanisms.

   Polar or ionic reactions with emphasis on SN1 and SN2 reactions, free radical reactions, molecular or four-center reactions.

6. Structure-Reactivity Relationships

   Electronic (inductive and resonance) effects. The Hammett equation and the Brönsted catalytic law. Steric effects in reactivity.

7. Properties of Medicinal Agents

   The various classes of medicinal agents, hydrocarbons, alcohols, inorganic and organic acids, nitrogen compounds, etc. are discussed in terms of the following properties.

   a. Physical Properties.

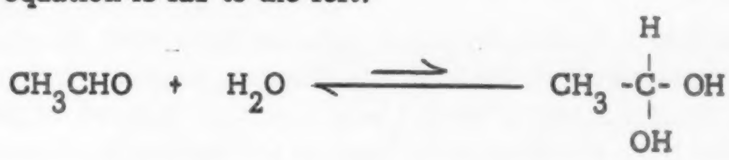
      Emphasis on those properties of pharmaceutical interest which result from the characteristic functional group of that class and its interaction with the rest of the molecule and other molecules. Examples are solubility, viscosity, absorption of radiant energy, acid-base strength.

   b. Chemical Properties.

      Emphasis on the functional groups which are important in formulation, stabilization, and mode of pharmacological action. The mechanism of each reaction should be fully discussed making use of the theoretical background developed in the earlier topics of the course.

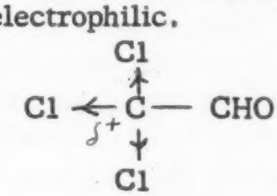
Approximately one-third of the course may be devoted to the first 6 topics of the outline and the remaining time to topic 7, i.e. the physical and chemical properties of medicinal agents with applications to formulation, stabilization, and pharmacological action of the various compounds and classes.

Qualitative Examples. The stability of chloral hydrate may be used as a qualitative example of the application of electronic principles to the discussion of medicinal agents. In general, aldehydes do not form stable hydrates; the equilibrium in the following equation is far to the left.

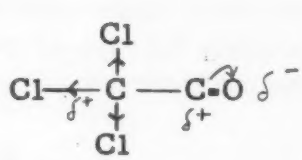


However, chloral (trichloroacetaldehyde) readily forms the stable chloral hydrate. This may be explained by the following mechanism.

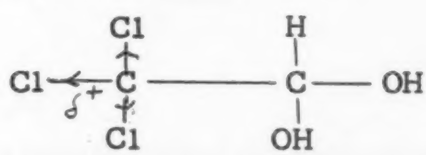
The inductive withdrawal of the three electronegative chlorine atoms makes the carbon to which they are attached electrophilic.



At the same time the electron withdrawal of the oxygen of the carbonyl makes the adjacent carbon atom electrophilic.



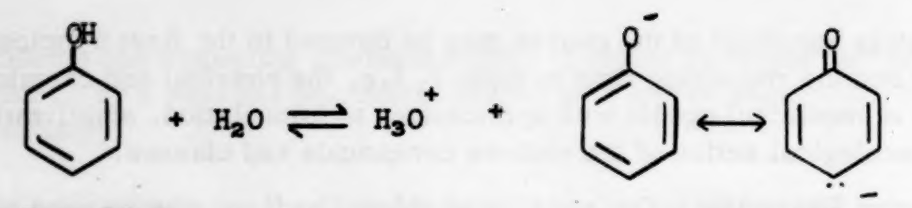
This creates an unstable system of two positive charges next to each other. However, the molecule can be stabilized by the formation of a hydrate with accompanying destruction of one of the electrophilic centers.



In general, two carbons adjacent, each having a fractional positive charge, easily add water to form a hydrate in which one carbon atom no longer has this charge. This "adjacent charge rule" is discussed by Pauling, Nature dof the Chemical Bond, p. 199.

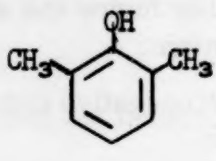
A second example involves the inductive, resonance and steric effects as they influence the acidity of phenols.

(a) Resonance and inductive effects. The acidity of phenol is explained in terms of the resonance stabilization of the phenolate ion and the inductive effect of the aromatic ring. Phenol has pKa of 10.0.



pKa = 10.0   resonance forms

It has been shown that 2,6-dimethylation reduces the acidity (increases the pKa) of phenol by 0.6 units owing to the electron donating property or positive inductive (+I) effect of the electropositive methyl substituents. Hyperconjugative effects are also influential here and may be brought to the student's attention if desired.



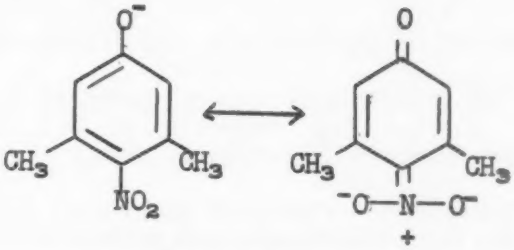
$pK_a = 10.6$

The relative acidities of the barbiturates might also be discussed at this point. The acidity of phenobarbital (pKa 7.41) is greater than that of barbital (pKa 7.90) because the more electronegative phenyl group is substituted for the ethyl group producing an electron withdrawal (-I) effect on the barbituric acid molecule.

The addition of a nitro group in the para position of phenol, or in the para position of the dimethyl derivative shown above, results in an increase of acidity of 2.8 and 3.4 units respectively because of the great resonance stabilization of the p-nitrophenolate ion and the inductive effect of the p-nitro group.

$pK_a = 7.2$ $pK_a = 7.2$

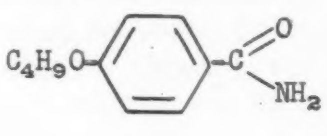
(b) Steric effect. However, when the methyl groups are substituted in the 3,5 positions, they prevent the nitro group from assuming coplanarity relative to the benzene ring, which is required for resonance. Accordingly, the acidity is decreased by 1 pKa unit (from pKa 7.2 to 8.2) by the steric inhibition of resonance.



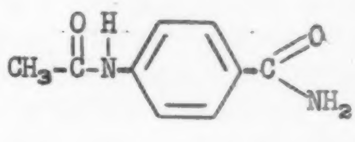
pKa = 8.2

A Quantitative Example Involving the Hammett Equation.

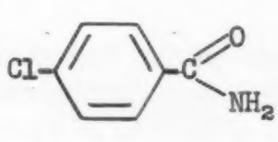
As an example of how one of these topics may be treated quantatively and applied to a pharmaceutical problem, let us consider three newly synthesized compounds for use as dental anesthetics. All are found to have the same therapeutic activity. We wish to make two alcoholic preparations, one buffered at a pH of 5 and the other at a pH of 9 for certain conditions where acid and alkaline solutions are required in dental work. The three compounds are



I



II



III

The quantitative relationship between the structure of para or meta substituted derivatives of benzene and reactivity of the compounds is given by the Hammett equation

$$\log \frac{k}{k_o} = \rho \sigma \qquad (1)$$

The σ is a constant for each substituent and gives a measure of its polar (inductive and resonance) effects on reactivity, while ρ is a reaction constant and indicates the effect of polar substituents on a given reaction series. The ρ and σ values for the compounds under discussion are given in Table 1. From these and equation (1) it is possible to compute the rate of hydrolysis of the compounds in alkaline and acid media. The specific rate constants, from which the half lives can be obtained, are also listed in Table 1.

Table 1. Data for hydrolysis of dental anesthetics in 60% ethanol*

Compound	ρ at 52.5°	σ	log k_O	log k	k (liter/mole-sec)
		Basic Hydrolysis			
I	1.364	-0.320	-5.190	-5.627	2.36×10^{-6}
II	1.364	-0.015	-5.190	-5.211	6.15×10^{-6}
III	1.364	+0.227	-5.190	-4.880	13.18×10^{-6}
		Acid Hydrolysis			
I	-0.483	-0.320	-5.606	-5.451	3.54×10^{-6}
II	-0.483	-0.015	-5.606	-5.599	2.52×10^{-6}
III	-0.483	+0.227	-5.606	-5.716	1.92×10^{-6}

From these results it is observed that compound I should be used at pH 9 since it exhibits a six-fold decrease in rate of decomposition over that of compound III. At a pH of 5, on the other hand, compound III shows a two fold reduction in rate over compound I. Hence compound I would be made up in an alkaline vehicle and compound III in an acid vehicle as potent, relatively stable, dental anesthetics. When the data are available at several temperatures, it is possible by an extrapolation of the results to 25° C to predict the actual stability (shelf-life) of the products at room temperature.

The teacher, of course, must inform the students of the limitations of the Hammett equation, and the modifications that must be employed when dealing with ortho substituents and with aliphatic compounds.

* Jaffe, H. H., Chem. Rev. 53, 191 (1953)

The following bibliography should be helpful for those who desire to develop a course in medicinal chemistry along these lines.

1. Alexander, E. R. Principles of Ionic Organic Reactions, J. Wiley, 1951.
2. Hammett, L. P., Physical Organic Chemistry, McGraw-Hill, 1940.
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4. Ferguson, L. N., Electronic Structures in Organic Chemistry, Prentice-Hall, 1952.
5. Newman, M. S., Steric Effects in Organic Chemistry, J. Wiley, 1956
6. Braude, E. A. and F. C. Nachod, Determination of Organic Structures by Physical Methods, Academic Press Inc., 1955.
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8. Ingold, C. K., Structure and Mechanism in Organic Chemistry, Cornell University Press, 1953.

In conclusion it should be observed that pharmacy is now entering a period when the pharmacist, pharmaceutical chemist and pharmacologist will apply more fundamental physical chemical principles in contrast to the predominantly empirical methods of the past. Not only must we develop a curriculum with provision for more general education and a better integration of scientific and professional subjects, but we will also be required to make many modifications in our course content and teaching techniques in order to fulfill the course objectives in the years ahead. Some suggested changes in course content and teaching methods have been presented in this paper.

DISCUSSION

Dr. Smissman discussed the variability of sigma values according to orientation of substituents, or their presence in aliphatic rather than aromatic systems. He pointed out the danger of over-simplification when discussing an isolated case.

Dr. Martin pointed out that discrepancies resulting from steric effects present a good opportunity for discussion of such effects. He enlarged on the use of the Hammett equation and its limitations as a means of stimulating the interest of students and demonstrating that much remains to be discovered or explained.

Dr. Smissman wondered if the course were elective or required.

Dr. Martin pointed out that the course had been proposed but had not been presented.

A discussion of physical pharmacy followed, and the need for stressing quantitative aspects was pointed out. There appeared to be a difference of opinion in respect to the content and integration of courses in pharmaceutical preparations and physical pharmacy, as well as physical chemistry.

SYLLABUS OF A COURSE IN BIOLOGICAL CHEMISTRY

FOR PHARMACY STUDENTS

Ernst R. Kirch

In 1946, Dr. H. B. Lewis[1], speaking before a conference of teachers of chemistry, discussed the place and the future of biochemistry in the pharmacy curriculum. At that time, he expressed the conviction that the "inclusion of biochemistry as a required subject would be necessary within 10 years unless the trends in professional pharmacy and medicine changed materially." His presentation at that time was based primarily on a survey of courses in biochemistry given in the colleges of pharmacy in the U. S. A. and made at the request of the syllabus committee. Very little, if anything, can be added today except to emphasize the point of view expressed in 1946.

It was the almost unanimous opinion of those with whom the problem was discussed that some formal training in biochemistry was desirable for students in pharmacy. The objection - if any - to the inclusion of biological chemistry as a required subject in the curriculum of pharmacy was a matter of scheduling. Even in going from a 4 to a 5 year course in Pharmacy some educators seem to believe that there is not enough time for biochemistry in the curriculum, while other schools devote a whole year to the subject.

I would like to propose a one quarter or a one semester course of biochemistry for Pharmacy students consisting of approximately 32 hours of lectures and about 40-44 hours of laboratory work.

Before I do go into details, I would like to go back and state some of the objectives of the course.

Physiological- or Bio-chemistry concerns itself primarily with the chemical aspects of living matter - of cell life. The rapid growth of this subject as a science is intimately related to the development of theoretical chemistry - especially organic and physical chemistry. While it is true that biochemistry has drawn largely from these sources, it is especially true that it has in turn contributed to every phase of biological sciences.

A considerable portion of the present day research in microbiology, pathology, pharmacology, and physiology either has a chemical basis or depends upon biochemical methods of study.

There are actually no boundaries which separate physiology from biochemistry and biochemistry from biophysics.

The student of biochemistry should be equipped with a knowledge of fundamental principles. He must learn to apply these principles to the study of physiological processes. From a biochemical point of view, the students should be interested in the numerous reactions which occur in every cell and that these reactions take place

simultaneously. As pharmacists, we are interested not only in the normal reactions but also in the abnormal reactions which occur during certain diseases and the possible effect of remedial agents on these actions.

Most courses in biochemistry start with the conventional treatment of carbohydrates, fats, and proteins. This is followed by a discussion of such topics as buffers, osmotic pressure, colloids, and various other topics belonging to courses in physical chemistry.

Why repeat these phases of organic and physical chemistry? True as is the case in a number of medical and dental colleges where the student comes with a short course of organic and no course in physical chemistry or even quantitative analysis, then it is necessary to include these phases in the course in biological chemistry. But in the case of the student in pharmacy, this repetition is superfluous. He has had or should have had a complete (full year) course of organic chemistry, at least a one quarter or one semester course in quantitative analysis, and in physical chemistry. One can then begin the course in biochemistry with a discussion of enzymes and vitamins followed by metabolism of carbohydrates, fats and proteins.

From what has already been said, it will, I hope, be apparent that it is my conviction that a strong course in biochemistry should be available to the student in pharmacy. I do not propose to condense the two semester or two quarter conventional course in biochemistry to a one quarter or one semester course.

What is proposed is a better coordination of certain course work covered in the courses already referred to, namely, organic chemistry, quantitative analysis, physical chemistry, and physiology.

I repeat there is no need in covering again the basic reactions of carbohydrates, fats, and proteins, nor topics such as buffers, osmotic pressure and another physical phenomena. The same can be said about topics properly belonging to physiology, such as circulation, water balance, acid-base balance, respiration and hormones, digestion, and maybe some others. One can instead concentrate on such topics which, in my opinion, properly belong in a course of biochemistry.

While credit must and will vary according to the opportunities that are available in each institution, it would seem that under the proposed outline the course would consist of 3 lectures and of about 3 hours of laboratory per week (3 lectures and 4 hours of laboratory per week for the quarter system). It is recognized that this is less than the conventional standard courses in medical colleges. I would like to point out again that the proposed course of about 33 lectures, when utilized properly and coordinated with material covered in other courses, should be sufficient to present that subject matter belonging to the field of biochemistry proper, especially as applied to pharmacy. As far as laboratory work is concerned, it is admitted by many educators that with the superior background in chemistry available to students of pharmacy, the smaller number of hours may be used with greater efficiency than in the longer medical course.

The same can be said, I believe, for the lecture content of the course.

Before presenting a topic outline for the course in biochemistry, one should outline at least those parts of the course in organic and in physical chemistry which have definite application to biochemistry and are some of the topics covered in the usual courses of biochemistry.

A. Organic Chemistry

1. Chemistry of Carbohydrates
Classification -Nomenclature
Configuration and proof of structure
Reactions of and tests for carbohydrates
(About 7 Lectures)

2. Chemistry of Lipids
Classification - Saponifiable - Nonsaponfiable
Reactions and tests
(About 4 Lectures)

3. Chemistry of Proteins
Definition - General properties
Classification of (a) amino acids, (b) proteins, (c) peptides.
Structure and reaction of proteins
Tests for amino acids and proteins
Colloidal properties of proteins
(About 6 - 8 Lectures)

B. Physical Chemistry

In addition to the regular topics of physical chemistry, such as electrolyte dissociation, acid-base equilibrium and buffer action (Henderson-Hasselbalch Equation), the following material presented in the course of physical chemistry is believed to have definite application to biological systems. (About 7 Lectures)

1. Blood as Physicochemical system. The properties of carbon dioxide in aqueous solution. The properties of the serum proteins and of hemoglobin. The oxygen and carbon dioxide dissociation curves of blood.

2. The equilibrium between cells and plasma. Electrolyte, and acid-base equilibrium of blood. pH of cells and plasma. Cell volume and osmotic pressure.

3. Oxidation and reduction in biological processes. Respiratory enzymes. Hydrogen transport reactions. Electron transport reactions.

4. Redox potentials of biological systems. Free energy changes of oxidation reduction reactions and relation to redox potential.

5. Reaction Kinetics. The velocity constant. Zero order, first order and second order reactions. The effect of temperature on reaction rates. Activation energy. Kinetic theory of reaction rates.

6. Catalysis. Enzymes. The Michaelis Mentin theory of enzyme catalysis.

C. The course in human physiology would cover the topics such as blood and the internal environment, blood clotting, mechanism and function of breathing, oxygen and carbon dioxide exchange, hormones, kidney function and urine. These and perhaps other topics are presented to a better advantage in this course.

D. The course in biochemistry would then cover the following topics:

1- (1) Introduction and brief review statement of carbohydrates, fats and proteins.

2-3 (2) Enzymes

4-7 (4) Vitamins

8 (1) Metabolism - general introduction, techniques.

9-10 (2) Biological oxidations.

11-14 (4) Digestion and Metabolism of Carbohydrates

15-17 (3) Digestion and Metabolism of Fats

18-22 (5) Digestion and Metabolism of Proteins and Nucleic Acids

23-24 (2) Blood - Hemoglobin

25 (1) Inorganic Metabolism

26-27 (2) Nutrition and Energy

28-29 (2) Antimetabolites

30-31 (2) Detoxication

32-33 (2) Hormones in general or any special topic

The time devoted to each of the topics should be regarded as a general guide only. It is well recognized that some realignment has to be made. In general, however, I believe that the material presented in biochemistry as proposed and coordinated with the other courses will offer the student in pharmacy a course in biochemistry that will be of excellent quality.

[1] Lewis, H. B.; Biochemistry in the Pharmacy Curriculum. Optional or Required Subject, Am. J. Pharm. Ed. 11, 119-25 (1947).

DISCUSSION

Dr. Huitric wondered whether such a short basic course would prepare students for graduate study in biochemistry.

Dr. Kirch recommended the standard basic course in biochemistry for potential graduate students. The short basic course is adequate for other purposes when students are instructed in topics related to biochemistry (carbohydrates, etc.) in organic chemistry courses.

Dr. Lee indicated that a four credit course in biochemistry is inadequate even in conjunction with courses in organic chemistry and the chemistry of natural products. A course in protein chemistry including structure, respiration, acid-base balance, enzyme aspects, role of metals, oxidation-reduction, the Hammett equation, etc. is necessary for an understanding of intermediate metabolism, and in preparation for the course in organic medicinal products. The significance of the Michaelis constant serves to introduce the student to the Lineweaver-Burk equation and the competitive and non-competitive inhibition aspects which are necessary for understanding of pharmacology and the chemistry of organic medicinal products. The questions of discussing the "nutrition aspect of Pharmacy" was raised.

Dr. Kirch mentioned an elective course in natural products which includes information on vitamins that is not covered in the biochemistry course.

Dr. Lee discussed the biochemical aspects of vitamins that are covered in a course on vitamins and hormones. Nowhere in the curriculum, however, are the nutritional aspects necessary for the dispensing of vitamins discussed.

Dr. Kirch suggested that the two lectures devoted to nutrition provides more information than that offered in the medical courses in which metabolism rather than nutrition is emphasized.

Dr. Lee's comment on mineral metabolism prompted Dr. Kirch's suggestion that some of material can only be outlined in the hope that the student will acquire the necessary information from textbooks. Too much should not be covered in the course which should be adequately presented in other courses such as physiology and physical chemistry.

Dr. Gisvold commented that there is considerable redundancy in the interdisciplinary courses, which could be resolved by a better integration of the course syllabi.

A COURSE IN FORENSIC CHEMISTRY

Arthur J. McBay

Forensic chemistry is a branch of science which deals with the physical and chemical examination of materials for presentation to the courts as evidence. Forensic chemists must be prepared to perform many diversified tasks, since the laboratories that employ them vary greatly in the services demanded. In those laboratories which serve medical examiners and coroners, the activities are restricted mainly to toxicological examinations and rarely deal with other phases of forensic chemistry. However, the duties of other laboratories may include the examination of physical evidence, the identification of drugs and the analysis of urines and saliva from race horses and dogs.

A pharmaceutical education makes an excellent foundation for a person interested in forensic sciences. The identification of drugs is relatively easy for a person who has had the usual courses in the pharmacy curriculum. The analyses of blood and urine are usually included in biochemistry laboratory. In microbiology, elementary work on blood identification and grouping is presented. Microscopy, which is essential to the criminalist is a fundamental of plant science, which in turn allows the pharmacist to recognize plant drugs. Familiarity with poisonous materials is gained in chemistry, pharmacy, pharmacognosy, pharmacology, as well as in courses which include newer drugs, chemicals and pesticides.

For the pharmacy curriculum it would be advisable to limit the course in forensic chemistry to the field of toxicology. Those taking the training would be apt to find a knowledge of toxicology more useful. With their background they would find no great difficulty in learning the other techniques of forensic chemistry should they find them needed. Toxicology is the science which deals with detection of poisonous agents and their effects. There is only one profession for which the members are trained in both these fields and that is pharmacy. If this fundamental knowledge is expanded to include the toxicology of more substances and also to introduce a few specialized subjects, then the person with this training will be well equipped to serve as a toxicologist. One of the major problems in toxicology is the identification of the newer drugs in biological materials. The person with a pharmacy background is aware of what drugs are being used and has knowledge of their properties.

Training in toxicology could serve the pharmacist in many ways. He could be a valuable member of the staff of a poison information center. If he is a hospital pharmacist, his advice on toxicology would be sought by many. Clinical chemistry is reaching a point where the field requires many highly trained individuals. The food and drug laboratories are seeking personnel with this background. Other laboratories requiring people with this training are those of industrial hygiene, crime detection and racing chemistry laboratories. Most of the larger pharmaceutical manufacturers now have their own toxicology laboratories; the smaller ones are served by consulting laboratories. There is an increasing need for

experts to provide scientific knowledge for the defense in many of our court trials.

Opportunities in the field have been appearing in increasing numbers in the last decade. As more states have recognized the importance of adequate investigation of sudden and unexplained deaths, medical examiners have been appointed. In the course of their medico-legal training they have had available a good toxicological laboratory and are anxious to organize and staff one of their own. Since there are very few organized courses available in the field of toxicology, it would be a distinct service to make these opportunities available in the pharmacy graduate curriculum. Salaries in these positions, in general, are equal to or better than those available in pharmacy positions.

Research opportunities in this field are unlimited. Routine experience will, of necessity, show means of improving existing procedures or of developing better ones. Research problems concerning methods of detection, identification, and quantitation of drugs in biological materials would be excellent challenges for graduate students in the college of pharmacy.

TABLE I

REPORT OF A TOXICOLOGICAL LABORATORY (1)

	%		%
Alcohol	60	Morphine	6
Barbiturate	11	Chlorides	4
Carbon monoxide	8	Lead	1
Total	79	Total	11

Less than 1% (in decreasing order) - Paraldehyde, salicylates, Formaldehyde, silica, cyanides, phosphorus, chloral hydrate, Demerol, ether, methanol, mercury, arsenic and Dilantin. The above list includes about 97% of the determinations.

From Table I it is apparent that about 90% of the work of the toxicologist is making analyses for about half a dozen substances. Certainly these should be included as laboratory experiments for any contemplated course. In analyzing for these substances, a student would obtain sufficient familiarity with the methods and problems of toxicology so that he should be able to apply himself to the analyses of other substances less frequently encountered. Extension of the laboratory exercises to include the identification of semen and sperm and the identification and grouping of blood would give sufficient background for a medical examiner's toxicologist. Training in criminalistics could follow by including exercises in the examination of physical evidence if it were desired to offer more training.

Alcohol

Since ethyl alcohol is a factor in the majority of homicides and suicides and in about half of the automobile fatalities, it is one of the most frequent and important determinations that the toxicologist is required to make. The method of determination will depend upon the number of samples to be processed and on what chemically related materials must also be determined. For screening a large number of blood samples a micro diffusion procedure (2) is most useful. The classical method uses acid-dichromate oxidation of the steam distillate followed by sodium hydroxide titration of the distilled acetic acid (3). Instruments which measure breath alcohol are in widespread use by police agencies and the toxicologist should be familiar with them. The micro diffusion procedure is also useful in the determination of methanol, isopropanol, acetone, acetaldehyde, formaldehyde, cyanide, carbon monoxide and halogenated hydrocarbons (2).

Barbiturates

Barbiturates must not only be quantitated but also must be identified as phenobarbital or as rapid-acting barbiturates; when both are present, the relative amounts of each must be determined. Small therapeutic amounts of phenobarbital taken daily may produce a blood barbiturate level of about 1 mgm. %. This same level of rapid-acting barbiturate in the blood is sufficient to attribute death to barbiturate poisoning. Barbiturates may be quantitated in biological materials by means of ultraviolet spectrophotometry following their extraction as organic acids. (4) (5). Probably the best way to both quantitate and identify barbiturates is one which combines both spectrophotometry and paper chromatography (6).

Carbon Monoxide

Carbonylhemoglobin may be determined by means of colorimetry (7) or by the reaction with palladium chloride (2). The latter method is not too useful for low blood carbon monoxide concentrations.

Chlorides

The determination of chlorides in blood removed from the two chambers of the heart has been useful in evaluating salt water drownings but is of questionable value for fresh water drownings. Blood specific gravities (8) are reported to be more valuable in evaluating both types of drowning.

Organic bases

Organic bases, except morphine and heroin, may be extracted from biological materials. The ultraviolet spectra of the appropriate extracts are used for the identification and quantitation of the organic bases (9). Some of the newer tranquilizers are extracted and must be separated and determined. Special methods must be used for morphine and heroin. (10).

Lead

Lead may be determined by a dithizone procedure (11).

Other substances

Methods for determinations of the other substances less frequently encountered may be found in the texts on Legal Medicine (12, 13).

Identification of blood and seminal fluid should be studied in the course in forensic chemistry. Blood may be detected by the benzidine test as well as by other tests (14), and precipitin tests applied to determine the species origin. Grouping of blood stains is of equal importance (15).

Seminal fluid is identified by means of the acid phosphatase test (16). Slides should be prepared and examined microscopically for the presence of spermatozoa.

For special projects there are many techniques that may prove useful, some of these are:

Tests for gunpowder residue (17)
Examination of trace evidence such as: hair, fibers, paint and toolmarks (14).

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CHALLENGING THE SUPERIOR STUDENT IN UNDERGRADUATE INSTRUCTIONS

J. William Buchta

For education, the past year has been one of interrogation, introspection and sometimes inquisition. The period just ahead may be a year or years of decision. Probably at no time has the American school system been under such critical examination and criticism. Education is a field where one man's opinion is usually better than that of the next, at least that appears to be the situation today, when we hear such a chorus of voices, some praising, some condemning, all saying what should be done. But that is what we expect in America. Our schools cannot and do not ordinarily rise much above nor are they allowed to fall much below the level set by the society in which they live.

As a nation we have been adding to our population about 7,500 souls per day since 1950. We have thrown a tremendous responsibility on our educational system. In 1900 approximately 15% of the high school age group were in high school. Today that figure is 80%. About 60% of the youths of graduation age graduated from high school in 1956. The high school has become the common school of the land. In 1900 approximately 4% of the college age group were in college. Today it is more than 30%. In fact, in many localities more than 50% of the high school graduates enter some institutions of higher learning. In 1956 one out of four United States citizens was enrolled in some formal school program.

But in all this relatively sudden expansion, a growth that has taken place in our lifetime, we as American citizens are dedicated to the rights, privileges and value of the individual. The most recent report on our educational problems is the so-called "Rockefeller Report" on Education. The report is entitled, "The Pursuit of Excellence - Education and the Future of America." In this we read,

"The greatness of a nation may be manifested in many ways - in its purpose, its courage, its moral responsibility, its cultural and scientific eminence, the tenor of its daily life. But ultimately the source of its greatness is in the individuals who constitute the living substance of the nation.

"A concern for the realization of individual potentialities is deeply rooted in our moral heritage, our political philosophy, and the texture of our daily customs. It is at the root of our efforts to eliminate poverty and slums at home and to combat disease and disaster throughout the world. The enthusiasm with which Americans plunge into projects for human betterment has been considered by some critics to be foolishly optimistic. But though we may have gone to extremes in a naive belief that we could cure all of mankind's ills, we need not be ashamed of the impulse. It springs from our deepest values. We do not believe that men were meant to live in degradation and we are foes of the poverty and ignorance which produces that result. We deplore the destruction of human potentialities through disease, and we are prepared to fight such destruction wherever we meet it. We believe that man--by virture of his humanity--should live in the light of reason, exercise moral responsibility, and be free to develop to the full the talents that are in him.

"Our devotion to a free society can only be understood in terms of these values. It is the only form of society that puts at the very top of its agenda the opportunity of the individual to develop his potentialities. It is the declared enemy of every condition that stunts the intellectual, moral and spiritual growth of the individual. No society has ever fully succeeded in living up to the stern ideals that a free people set themselves. But only a free society can even address itself to that demanding task.

"There is no more searching or difficult problems for a free people than to identify, nurture and wisely use its own talents. Indeed, on its ability to solve this problem rests, at least in part, its fate as a free people. For a free society cannot commandeer talent: it must be true to its own vision of individual liberty. And yet at a time when we face problems of desperate gravity and complexity, an undiscovered talent, a wasted skill, a misapplied ability is a threat to the capacity of a free people to survive.

"But there is another and deeper reason why a free nation must cultivate its own human potential: such a task reflects the very purposes for which a free society exists. If our nation seeks to strengthen the opportunities for free men to develop their individual capacities and to inspire creative effort, our aim is as importantly that of widening and deepening the life purposes of our citizens as it is to add to the success of our national effort. A free society nurtures the individual not alone for the contribution he may make to the social effort, but also and primarily for the sake of the contribution he may make to his own realization and development."

The practical situation also demands that we give greater attention to the greatest resources we have - our youth. Our changing society is growing more complex and demanding. We need not only more but better talent. We live in a scientific and technological age. Automation is becoming a household word. In this connection we may again point out that while our science and technology grow in a cumulative fashion, the evolution of the human mind has not kept pace. Is there any evidence that we have greater innate abilities than those who lived 2000 years ago? Is our scientific society acquiring characteristics such that, because of human limitation, it cannot maintain itself? Are we, as have some biological species in the past, developing lethal characteristics? Do we have our Frankenstein? To illustrate the situation on a more mundane level, we point out that the housewife needs to be a master mechanic to manage her kitchen and laundry, the automobile repairman needs to be an engineer to understand an automatic transmission. The jet pilot is limited by the response time of his nervous system. No recent improvements in that system have been announced!

"Suppose the 10% of the high school graduates with ability, who do not enter college, would enter college,--would our problems be solved? Would our difficulties be removed by an acceleration which reduced the period of education up to the college level by two years? Would the total demands of our scientific and politically and socially complex era be met by these changes or even by any that we can make in education? The situation is illustrated by a statement of the Commission on "Human Resources and Advanced Training." During the past half century the number of school teachers in the United States has increased

1 1/4 times as rapidly as the total population. The number of professional health workers has increased 2 1/2 times as rapidly, the number of engineers 5 times, and the number of scientists 10 times. With a population twice as large as in 1900, the nation employs four times as many men and women in professional fields."

Possibly to meet the present and future situation we shall need to make some adjustment in our genes! Instead of charging the educational system with failure to meet the needs of the present day, as is often done, we should examine some possible causes that may be responsible for our situation. Does the needed number of persons with the required potential qualifications exist? Is there any firmer basis for believing we can make one third of our college young people competent scientists than thinking we can make one third of them poets? Or that we can increase the number of scientists by 30% any easier than we can step up the production of poets by 30%? In any case it is clear we must make the maximum use of the talent our people have.

Now that we have presented an overall view and expressed our concern for the individual and the full development of his potentialities, let us examine some practical and concrete measures that can be taken to do this.

Today we hear many discussions and arguments on quanity versus quality in education. They are based on the assumption that we can have one and not the other. But in our society, with its wealth and resources, we can have both. We need both. We need only to decide what is wanted, to examine our scale of values when we decide to spend on education, highways, cosmetics or alcoholic beverages.

Let us now examine in some detail the various ways we can challenge the gifted undergraduate. First there is the matter of identification. With our large number of students we depend more and more on specific tests. And this procedure has not been a failure. But always we should recognize that a test tests what a test tests. Giving it a name does not necessarily identify what is tested. Tests of all kinds should be looked upon as aids, not automatic devices for making our decisions. And certainly a major decision should seldom if ever be based on the results of <u>one</u> test.

Our British cousins believe they can make decision on the future course of study for a child by tests and standing when the child is about eleven years of age. We usually postpone that decision until the student is seven years older, and even at this age we make no rigid decision. If the youth is not accepted by one educational institution, he usually can find another that will take him. The initial admission to college is not as difficult as the transfer from one institution to another, once he has failed in the first.

I believe it fair to say that the superior student can be identified when he is an entering freshman. The high school rank, (based on four years of testing in the classroom), tests prepared by the College Entrance Examination Board, and the American Council on Education, tests devised by local groups often in particular fields or with limited objectives can be used. However, I urge caution in assuming any <u>one</u> of them is a completely valid criterion in making a decision that has lifetime implications for an individual student.

It is generally agreed that tests such as we have mentioned, plus the performance during the first year in college, give a more valid indication of superior native ability and the motivation to use it, than any other combination of measure we now have, but that does not mean we should defer all special attention to those that may have higher potentialities until after the first year in college. After all we have our freshman squad on the football field!

The job of challenging the entering freshman of high ability is in these days of large enrollment, not a simple one. But it is becoming increasingly recognized as important. The inter University Committee on the superior student, with headquarters at the University of Colorado, Boulder, Colorado, is giving much attention to the freshman year. In the publication of this committee, entitled, "The Superior Student," Dean Waggoner of Kansas writes,

"Many department honors programs at the junior-senior level have had a tendency to languish and to suffer from a lack of vigorous student interest. The lack of student interest, I think, grows largely out of the student's experiences during his first two years of college. If the upper division honors programs are to flourish, the student's first two years must be of a kind to bring him to the beginning of his junior year both prepared and motivated to volunteer for the independent study and extra work that the departmental honors programs require.

Then later he says,

"Clearly, there is need to identify the freshman of outstanding ability as he begins his university work. The task is actually done already in most universities through well-established scholarship programs, though this information is often neglected by the academic division of the university. Anyone missed by these earlier devices can be identified through careful scrutiny of both high school records and the usual orientation tests which almost all universities give. Really outstanding students identified in any of these ways then deserve outstanding academic advisers, advisers who are given the authority to waive the usual academic regulations to the extent that is necessary in order that the gifted student be placed in a program of courses that challenge his full ability. These steps must be taken as the freshman enters the university; not after he has a semester or a year to adjust to the conventional pace of the average student."

Placing the outstanding student in a special section of a multi-sectioned class is a feasible method of recognizing the better student and giving him an opportunity to compete with his equals. It also allows special treatment in one area and not necessarily in another. But even in institutions where special sections are not organized, extra assignments or awards for going beyond the mere passing of a course can be made. The award may be only the recognition by the teacher that the student has excelled. The extra assignment may be at least one question of more than ordinary difficulty in each examination or assignment. The inclusion of these need not be unfair to the majority of a large class since few will complete them and the instructor need not penalize the class as a whole for not doing the very difficult questions. I can recommend this procedure from personal experience with it.

In the debate on acceleration versus enrichment of curriculum for the superior student, I take the side of a broader and a more complete curriculum for those able to master it rather than earlier graduation. Sometimes it seems to me we tend to hand on to the less talented and to push out of the school those who can go farther. We seem to strive to have all attain a given level rather than to urge all to go as far as they can in the time available.

What are the effects of the esteem with which the highly competent are held by their classmates and the public at large? The attitudes of the public and its effects are hard to measure. I am not convinced the general public belittles intelligence and wisdom as much as we are often told it does. It is true that an Elvis Presley or a football star may gain more space in the daily press and may pay a higher income tax than most scholars, but that is not the only measure of regard society has for its members.

Certainly we in the academic world should not be guilty of holding the studious, the egg head, in lower repute than we do the average citizens. Let us in our classes exert efforts toward recognition and encouragement of those who can rise above the average.

The role of motivations is not always recognized. Emerson once said, "Our chief want in life is somebody who shall make us do what we can do."

How many of us who have gone on to graduate school can recall some encouragement or some bit of attention given by a teacher as the spark that urged us on? Possibly a major decision was made as a result of that teacher's interest. The teacher may have been in college, in high school, or in the grades.

The role of interest in illustrated by a story told me by a teacher in a remedial reading class. The boys in her class were would be hot-rod enthusiasts. She was having much trouble getting these youngsters to differentiate between words such as there and then, where and when, accept and except. One day she noted they were reading and apparently comprehending presumably more difficult words pertaining to automobiles. She then tried flash cards with Ford, Fiat, Chevrolet, Cadillac, DeSoto, Oldsmobile, Pontiac, Plymouth. They obtained a perfect score!

The successful teacher of all, including the gifted, must be able to excite the interest and best efforts of his students. He must inspire as well as instruct. I am sure this does not mean he should glamorize or make his subject easy by failing to probe its depths. Students will respond to procedures and subject matter that challenge their intellectual powers. All subjects ordinarily taught in college can and should be taught in a way that leads the student to stretch and to do this with some thrill. Certainly physics and pharmaceutical chemistry are in this category!

Is it democratic to give special attention to the intellectually elite? I would be the last to say the educational opportunities should be restricted to the elite. But, I would also balk at any policy which refused to provide them encouragement and opportunities comparable to their abilities. We recognize the fact that all cannot be on the first team on the playing field; why not give the same recognition in the classroom.

Again I wish to quote from the Rockefeller Report.

"It is now widely recognized that our society has given too little attention to the individual of unusual talent or potentialities. To make such an assertion is not to deplore the unprecedented time and money we have devoted to raising the general level of achievement. It would serve no purpose to replace our neglect of the gifted by neglect of everyone else. We are all too prone to such wild swings of the pendulum in our national life. We must learn to view these matters in a perspective which will permit us to repair one omission without creating others.

"It has not always been easy for Americans to think clearly about excellence. At the heart of the matter is a seeming paradox in democracy as we know it. On the one hand, ours is the form of society which says most convincingly, 'Let the best man win,' and rewards winners regardless of origin. On the other, it is the form of society which gives those who do not come out on top the widest latitide in rewriting the rules of the contest. It is crucial to understand this tug of war between equality and excellence in a democracy. When the rewriting of the rules is prompted by the standards of fair play, by elementary considerations of justice, by basic value judgments as to what sort of a 'best man' the society wants, democracy can have no quarrel with it. Indeed, it is the core process of a democracy. But when the rewriting of the rules is designed to banish excellence, to rule out distinguished attainment, to inhibit spirited individuals, then all who have a stake in the continued vitality of democracy must protest.

"Every democracy <u>must</u> encourage high individual performance. If it does not, it closes itself off from the main springs of its dynamism and talent and imagination, and the traditional democratic invitation to the individual to realize his full potentialities becomes meaningless. More, perhaps, than any other form of government, a democracy must maintain what Ralph Barton Perry has called "an express insistence upon quality and distinction." "

"With respect to the pursuit of excellence there are several considerations that we must keep firmly in mind.

"First, we must not make the mistake of adopting a narrow or constricting view of excellence. <u>Our conception of excellence must embrace many kinds of achievement at many levels</u>. There is no single scale or simple set of categories in terms of which to measure excellence. There is excellence in abstract intellectual activity, in art, in music, in managerial activities, in craftsmanship, in human relations, in technical work.

"Second, we must not assume that native capacity is the sole ingredient in superior performance. Excellence, as we shall later have occasion to note, is a product of ability and motivation and character. And the more one observes high performance in the dust and heat of daily life, the more one is likely to be impressed with the contribution made by the latter two ingredients.

"Finally, we must recognize that judgments of differences in talent are not judgments of differences in human worth.

"To sum up, it is possible for us to cultivate the ideal of excellence while retaining the moral values of equality. Whether we shall succeed in doing so is perhaps the fundamental issue in the development of our human resources. A challenge must be recognized before it can be met. Our society will have passed an important milestone of maturity when those who are the most enthusiastic proponents of a democratic way of life are also the most vigorous proponents of excellence."

We have discussed a general philosophy of education, one that places a high premium on the individual, insisted that it is not undemocratic to give special attention to the gifted, indicated that those with better than average abilities can be identified early and that in our diversified educational enterprise we can challenge the gifted to strive for higher goals and greater excellence. In fact, the unfinished business of democracy is the early identification of the able student and the provision and encouragement for his development at a pace that continually challenges him.

There is no unique way of challenging the gifted, but each of us may find his own way of doing it. High devotion to the teaching art will yield corresponding rewards. No discovery in the laboratory yields more satisfaction than the discovery in your class of a keen, discerning mind that turns to you as teacher in the highest, fullest sense of that word.

DISCUSSION

Dr. Webster commented that Dean Buchta "has not charted our course" and showed us our responsibility in dealing with the superior student. A teacher in a large university should take advantage of the opportunity to discern the superior student and to direct him towards greater development in the teacher's field or in some other. A student who cannot be motivated with respect to the scientific aspects of Pharmacy should be urged to find his peculiar genius in other phases, for example, social sciences or humanities.

Thursday Session

George L. Webster

Chairman

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THE TEACHER'S ROLE CONCERNING THE OBJECTIVES OF HIGHER EDUCATION

H. T. Morse

Mr. Chairman, Members of the Seminar on Pharmaceutical Chemistry:

We have been informed on reliable evidence that our colleges are facing, in the years immediately ahead, what has been called the "impending tidal wave of students." From some of the writings on this topic it would appear that we are to be inundated and almost overwhelmed by this tremendous wave resulting largely from sharply increasing birth rates after the war. Partly because of this fact, increasing attention has been focussed upon higher education. There are many aspects of it which are receiving renewed attention and scrutiny. Innumerable books and articles are appearing, for example, dealing not only with objectives of higher education, but with all aspects of the educational process beyond the high school level. We are witnessing also the development of courses in many colleges and universities concerned with the preparation of college teachers and with trends in American higher education.

Conferences, workshops, and seminars such as this one are being planned and held all over the country, in increasing numbers, devoting themselves to various aspects of higher education. Your own program for this seminar, I noted with considerable interest, has quite a number of topics scheduled which apparently bear no direct relationship to Pharmacy or to Pharmaceutical Chemistry. As I looked through this program I observed that you are having at various times this week addresses on such subjects as the "Evaluation of Student Performance", "Factors in the Learning Process", "Challenging the Superior Student", "Objectives of Higher Education", "Training of Prospective Teachers", and "Criteria for Teacher Evaluation". This seems to me to be an intelligently planned and varied program, and I sincerely hope that the efforts of Dean Hager and his associates on the planning committee will seem worthwhile to you, who are the consumer of these items.

One can hardly overemphasize the importance of higher education in modern American society. It is the first and inescapable phase in what might be called the great cycle of scholarship and intellectual life. And yet we are unfortunately confronted with an acute shortage of qualified personnel for our colleges and universities at the very time when the most severe demands will be made upon them because of the increasing numbers of students and the growing complexity of American and international life. The consequences of the teacher shortage have been underscored by the Educational Policies Commission in their recent publication, <u>Manpower</u> <u>and</u> <u>Education</u> as follows: "The teacher shortage has unique potency for breeding shortages in other areas where trained manpower is sorely needed. Failure to solve the problem of growing-scarcity versus increasing-demand in education will not only affect education; it will also affect adversely all the areas served by education. It will aggravate shortages generally and its effect will be cumulative."

We are concerned this morning with a crucial aspect of higher education, its goals or objectives, and the part which the teacher plays in determining and in realizing these objectives. One might presumably maintain that it should be reasonably simple to determine what the purposes of American Colleges and Universities are by looking into their catalogues or bulletins. Yet, as anyone knows who has engaged in this pleasant academic exercise, these statements of purpose and of intent are usually so high sounding and general that they sound like the proverbial road which is paved with good intentions. Further-

more, we are becoming increasingly aware that the objectives young men and young women have in going to college are not the same objectives the professors think they have or ought to have. That is to say, statements of objectives drawn up by members of the faculty are frequently rather idealistic, ivory towerish, and often far removed from reality. Perhaps this is as it should be. But reasons why students go to college, as indicated by their own statements, are largely ones which might be called relativistic, materialistic, and social.

It is accordingly necessary for us to keep in mind these distinctions, these differences of purpose, in assessing the role which we, as faculty members, may play most effectively. There is often, it seems to me, a close analogy between the objectives as stated in a catalog and those in actual practice with a so-called "memory by association" scheme which was proposed by the Canadian political scientist, Stephen Leacock. Leacock, as you may recall, was known as a humorist as well as a writer on serious matters of political economy. He has proposed what he called a new system to revolutionize learning. It was very simple, said Mr. Leacock, to remember things by making the proper association. For example, if one wanted to learn in sequence the names of the presidents of the United States, he had only to start with knowing the first one, and by making the right associations thereafter, he would be led into the sequence. Given the name Washington, for example, said Leacock, when we think of Washington we think of washing. When we think of washing, we think of Chinese, when we think of the Chinese we think of missionaries, when we think of missionaries we think of the Bible, when we think of the Bible we think of Adam, the first man in the Bible--and there you have it, Washington the first President and Adams the second President! Now we often read in the college catalogs that the purpose of higher education is to develop well-adjusted, well-rounded personalities and competent specialists. I sometimes feel that there is a "Leacock association" between the plans which the professor has for the conduct of the class, the actual situation in the classroom, the learning which goes on in the mind of the student, the behavior which is modified in the student's activities from that point on as a result of this learning, and the far distant and remote statements of objectives in the college catalog.

In order to analyze and examine for a few moments the role of the teacher in setting defensible objectives and in the realization of these objectives, we must, of course, break them down into somewhat more specific catagories. I should like to consider the role of the teacher in determining the objectives of higher education in three major catagories.

The first of these is in setting goals in terms of subject matter content. Now this purpose may seem all to obvious, and yet I should like to examine this point for a moment. Knowledge of subject matter is quite properly one of the major criteria in determining the effectiveness of a teacher or of a potential teacher. Sometimes it is considered to be the only role of the teacher, particularly the teacher at the college level. I have heard some of my respected colleagues say occasionally, "If a man knows his subject matter thoroughly, he can teach it well". I try to persuade these friends of mine (often without much success, I must admit) that they are speaking pontifically in bland ignorance of all the research that has been done on the teaching and learning process. Too narrow concentration on the factual aspects of subject

matter content teaching may well be commendable in part, but it might lead, perhaps, to some confusion. The story is told, for example, about a young assistant professor who had worked for some time on a major publication, and it so happened in this young man's life that the very day that his first book was received from the publisher, witnessed also the birth of his first child. He was walking rapidly across the campus that morning when one of his colleagues accosted him and said, "Well George, I heard the good news about you, and I certainly want to congratulate you!" The yound man, who quite naturally had uppermost in his mind the labors which had occupied his own attention and effort for a long period of time replied, "Well, thanks very much, but I just couldn't have done it without the help of some of my graduate students".

Unwillingness to venture beyond the boundaries of the thoroughly known and established subject field may sometimes lead one, I am afraid, into the spirit of the man who was riding with his young sone on a bus in New York City. As they traveled up Fifth Avenue toward Central Park, the boy rather excitedly said to his father who was reading the sports page of the daily paper, "Oh Daddy, Daddy, look over there, what's that building with the great big stone lions out front?" The father glanced rather indifferently out the window and said "Oh, I don't know". Pretty soon they came to a place where there were crowds of people and the youngster, still excited, said "Oh Daddy, Daddy, what's this place with all those fountains and all those people walking around?" The father glanced out again and said "Oh, I don't know". In a few moments, they came to the turn onto Central Parkway and the youngster, noting the big statue of a man on a horse in the center of the street there, said "Daddy, Daddy, who's that man up there on the horse?" Once again the father, with a quick glance, shrugged his shoulders and said "Oh, I don't know". The youngster, a little subdued by this time, finally said, "Daddy, do I bother you by asking so many questions?" The father, with a grand paternal smile turned to his offspring and said, "Why, of course not, son, how do you expect to learn things if you don't ask questions?"

The first and foremost type of content outcome with which we are concerned is, quite naturally, <u>facts</u>, the straws that go into the bricks that build the facade of learning. Simple as this seems, sometimes we may too readily judge that facts speak for themselves. In this connection I like the story about the mother who was having a birthday party and in buying the favors for the party thought that she would give her little girl, who was about in the fourth grade, an exercise in arithmetic. She asked the clerk how much these favors were and the clerk said, "These are five cents apiece". So the mother turned to the little girl and said, "Betsy, you have eleven little girls coming to the party and these favors are five cents apiece, how much is it going to cost? How much is eleven times five"? The little girl puzzled and puzzled and finally she said, "Well, Mommy, I don't know". And the mother said,"Why, you're in the fourth grade and you mean to tell me that you don't know how much five times eleven is?" "Oh yes, Mommy, I do, its fifty-five." And the mother said "Well, I can't understand it. When I asked you first you said you didn't know." And Betsy said, "Well, Mama, you asked me first what eleven times five was and we haven't had elevens yet, but we've had fives." Now even on that simple level it seems to me there is a moral for the teacher who would have learning function in the mind of the student.

In content outcomes we are concerned not only with facts and with understandings, but also with what has been called, by people who like to make these catagories, <u>skills</u>

or abilities. Now it would seem to be elaborating the obvious to suggest to a group of teachers of pharmaceutical chemistry that the development of skills is desirable as part of the learning process. We must concern ourselves, however, not only with the skill of hand, not only with the sharpness of eye, not only with accuracy and quickness of action, but with certain qualities of the mind, such as one that has received a great dear of emphasis lately, which we call critical thinking. In a democracy, in a country where the citizens must make many of the decisions which will safeguard the internal and external affairs of their country, it is imperative that the educated person must develop as fully as possible the ability to look at problems critically, analytically, and objectively. In the field of the social sciences increasing attention has been given, in the last few years, to ways and means of developing critical thinking as an adjunct to democratic citizenship. So crucial is this, not only in our present day, and in our present perilous circumstances, that even back in the time of Abraham Lincoln this sort of thing must have been what he had in mind when he spoke about the preservation of our liberties. Lincoln said, "What constitutes the bulwark of our liberty and independence? It is not our frowning battlements, our bristling seacoasts, our army and our navy. These are not our reliance against tyranny. All of these may be turned against us...Our reliance is in the love of liberty which God has planted in our bosoms. Our defense is in the spirit which prizes liberty as the heritage of all men, in all lands everywhere. Destroy this spirit and you have planted the seeds of despotism around your own doors."

A second major aspect of the objectives of higher education in which the teacher plays a significant role is that of providing interpretation and perspective on subject matter content. Subject matter in any field can be enriched, can be made more meaningful, can have a greater impact on the behavior of the student, if he is stimulated to develop a breadth of view, some understanding of trends, of relationships among major developments, of causes and of effects. When the student enters our class he is like a traveler in a strange land, a land which we ourselves have traversed many times. Were we literally riding through a country strange to him, but one which we had explored on all sides, far into the hinterland, we would surely wish to say to him, "Now beyond these hills the prairies begin; this stream is a tributary of the Mississippi River; in these woods there was at one time a large Indian settlement." We would not confine his attention only narrowly to the road ahead and the immediately adjacent area, or we would be considered a poor guide indeed.

There have been developments in higher education circles in recent years which have attempted to promote this concept of breadth as well as depth. Breadth not at the sacrifice of depth, but in order to reinforce it, to give the student what might be called a synoptic view, a wide and comprehensive view of areas of content and fields of study. In the undergraduate curriculum, courses of this kind which are primarily designed to provide such breadth are called "general education." They are often specially designed to cover, within a single course, broad segments of knowledge such as the social sciences, the natural sciences, and the humanities. Instead of a single subject or discipline within those fields, they stress the relationships among them, in content, in function, and in methodology, and their essential unity as fields of knowledge and means of analyzing and understanding human behavior, man's cultural

achievements, and the biological and physical world about us. But it is not necessary always to insist that general education follow a specific form, since there can well be something really more important which might be called the spirit of general education. In my estimation, and I have had many years of experience in association with this kind of program, I believe that in this as in many other things the spirit is more important than the form. This was further impressed upon me very sharply in the fall and winter of 1957 when I had the privilege of serving as one of a group of American educators working in India. My own particular assignment was to the University of Delhi, but all of us worked also through the Ministry of Education to help the Universities of India develop a broadened program for their undergraduate degrees. They were ostensibly interested in what we call general education, especially the interdisciplinary or integrated courses, but we soon discovered after we arrived that if we could help the Universities of India inculcate the spirit of general education, regardless of the particular form, this would be a major accomplishment indeed.

My assignment in India comes to mind frequently, because the impact of India on the westerner who goes there for the first time is little short of staggering. The travel books one might consult about this vast subcontinent, its peoples, and its civilization, will undoubtedly state that India is a land of contrast. This simple generalization is borne in upon one with startling reality when he first arrives and sojourns in this great country of southern Asia.

India is indeed, for example, a land of contrasting magnificance and squalor. On every hand there are vestiges of Oriental opulence and splendor such as the western mind can scarcely comprehend. One marvels at magnificent palaces which had quarters for five thousand servants and retainers. One stares amazed at temples which rise high up into the hot, blue Indian sky and which are carved upon every available inch of surface with intricate forms of flowers, of beasts, of men, in mute but skilful and time-consuming devotion to the numerous gods of Hinduism. Some of these mighty temples are roofed entirely with gold, the value of which can be determined only in terms of the number of tons of the precious metal which it takes to do this surfacing. Far beneath some of these temples, I have seen caverns of a thousand pillars which stretch away into the distant gloom, each pillar perhaps three or four feet square, intricately carved and in perfect alignment, cut by the most primitive tools out of the solid living rock, and in these great caverns even the ceremonial temple elephants seemed dwarfed into insignificance. At the entrances to shrines and mosques, I have seen great walls of marble which have been carefully incised and inlaid with semi-precious stones in floral and geometric designs which must have required infinite patience and almost indescribable care and skill.

In approaching some of the mosques one sees what appears to the western eye to be a great screen of lace hung along the entrance or stretched along the sides. As one approaches more closely, however, up the innumerable marble steps that lead to these impressive structures, he discovers to his surprise that this is not a great hanging of lace, rather it is a single sheet of marble, half to three quarters of an inch thick, which is so intricately and cunningly cut with open work that it resembles nothing so much as the finest lace.

One turns from the ostentatious evidence of wealth and opulence of the Nabobs, the Maharajahs and the rich of India to see in startling contrast the pitiful plight of all too many of the people. The worst off among them are the refugees from Pakistan, those who fled the terrors of a holy war at the time of partition back in 1947. In spite of desperate efforts by the government, they have not yet been satisfactorily absorbed into the economy or accommodated with land and living quarters. These poor souls labor in the broiling sun, carry indescribable burdens, and perform the most menial and filthy labors. They are beset with innumerable diseases, they are emaciated, undernourished, underfed. Fortunate, indeed, are those who have a little hut of crumbling mud, washed away periodically by the recurrent monsoon rains, into which they can crawl in the dark and damp night. Fortunate indeed are those who have two rags to cover their nakedness instead of one. Fortunate are those who can look forward to more than a single meager meal upon the morrow. The standard of living in India is the lowest in the world, and the westerner's heart is wrung constantly by the sights on every hand of the privation, of the poverty, of the desperate situation of these fine people. And yet, amazingly enough, they are philosophical in bearing their burdens. They are cheerful, they laugh, they joke, and one wonders how they can possibly continue to do so in view of the privation surrounding them and the bleak outlook ahead.

A second contrast in the Indian scene is that which is revealed by the position of women in this ancient society. Many Indian women are still often kept in a kind of seclusion which is called Purda among the Mohammedans, or Muslims, as they are called there. In the strictest and most traditional circles, a woman's face is never to be seen by any man except her husband after she is married. I have been told that in some of the villages this situation is carried to such fantastic extreme that a woman's given name is never mentioned by her husband or anyone else after the marriage. As one wanders about the crowded, muddy, dirty, smelling, but fascinating streets of old Indian towns, he occasionally sees these Muslim women wearing the burka, which is the hood fastened up over the top of the head, something like that of the Ku Klux Klan, but flat topped and gathered around the crown, falling down to the shoulders and sweeping all the way to the ground. Across the front, there is a broad coarse netting behind which their eyes gleam curiously at the world around them. Tradition requires them to wear these suffocating hoods to safeguard their faces and their sanctity from the eyes of strangers.

The Hindu women are not as much secluded, though even the Muslim women, we are told, are progressively being given greater freedom. I was interested, however, in the fact that even among my acquaintances there were vestiges of restrictions on the Hindu side. There were two Indian professors from the University of Delhi, who visited the University of Minnesota for two months before I went to India. These men were my hosts at Delhi and I was in their homes several times for dinner, even for breakfast at one time, and frequently for afternoon tea, which is one of the important institutions of India left as a legacy by the British. Yet I had not met the wife of one of my hosts at any of these times. During my stay I thought it would be nice to return some of this hospitality, so I invited the families of both my Indian professor friends to have a meal with me at the Cecil Hotel where I was staying. One of my hosts in saying that he himself would be glad to come said, "You must excuse my wife, you know she does not go out very much socially." I certainly knew it by this time, since I had been a couple of months in Delhi and I had not even seen this woman, although

I had often been in her home. But feeling that this explanation was not quite enough to satisfy the protocol of the situation, my Hindu friend went on to say, "You know my wife is so orthodox that she would not even enter a building where meat had been cooked."

Now here one has on one hand the seclusion of women in India because of tradition. But on the other hand I am sure that no women anywhere in the world are as thoroughly bejeweled, bedecked, bespangled and wear such gorgeous clothing as the women of India. One sees even the poor former outcasts or Harijans, as Ghandi called them, "children of God," performing the most menial labors in the streets. Sweeping up the dust, the dirt, the garbage, the refuse from the bullocks, from the camels, from the elephants, and even human refuse which is all too often also left in the street. And yet, on the ankles and arms of these women sweepers one will see band after band after band of sparkling silver, glass and gilded ornaments. They wear silver necklaces around their necks; many wear a diamond embedded in the left nostril. One asks himself, "How can this be"? Here are people who have no security, no home even, perhaps at night they lie sleeping on the cold, hard pavement. (If one takes a walk in an Indian city in the evening, he must of necessity keep stepping over sleeping bodies in all the gutters, in all the doorways, under the bridges, in the entrance ways, even out in the open in the summertime itself.) But these ornaments are, I understand, a form of security for these women. This is their dowry. It is what you or I would call money in the bank or an insurance policy, because this is the only reserve many of them have. They obviously cannot keep it in cash, so therefore, they wear their savings account in the form of adornment, which in case of crises can be sold to the silver-smith, although only the most grave crisis in the world would impel an Indian woman to part with her dowry. These are the poor. Among the wealthy the Indian women dress in the finest silks, jewels, and gold and silver brocades. They are a wonder and a delight to behold.

Among many others, there is a third contrast about which I may speak briefly. That is the contrast between Indian skill at individual artistry and their often unsuccessful attempts at making industrial products. The Indian craftsman, as anyone would agree who could observe the products of his skill, is one of the finest in the world. One gasps in bewildered amazement at their beautiful brocades and saris and scarves, scarves woven from the finest silk, which have intricate designs of gold, not made of gold thread at all but solid gold itself spun out to such incredible length and fineness that it can be woven as thread. I remember in particular a small ivory necklace which I purchased from an itinerant peddler for my wife. As I looked closely at this necklace, I noticed that the center piece was made of a small elephant very meticulously carved. There was also on each side four sacred animals--the deer, the cow, the lion, and the horse. Each one of these tiny beasts was carved in infinite detail. Every eye, every horn, every fang, every claw showed perfectly clearly although each one of these animals was a fourth of the size of the nail of your little finger. Between each one of them was a bead about the size of a small marble, which was hollowed out to give it texture. But as I looked more closely at these tiny perforations, no larger than the head of an ordinary pin, I noticed that every one of these hundreds of holes was made in the shape of a perfect star. And yet this work of infinite patience and skill sold for two or three dollars. Such skill as this is pitted against the products of their industry, which the Indians themselves criticize and complain about. They say

that their automobiles soon fall apart, that the chains fall off their bicycles, that the plumbing doesn't work, and that the Indian-made razor blades lose their edge after one or even half a shave. It seems to me that this apparent inconsistency perhaps may be explained by the fact that the Indian takes pride in the products which he makes individually, the creative pride of a master craftsman; but he doesn't like to share the credit for anything that he does. So when a worker attempts to make something on an assembly line in an industrial plant, he naturally feels that his personality is not involved in the end product. He evidently feels that it doesn't make any particular difference whether he does the job well or does not do the job well because the end product is so impersonal. In addition to this fact, Ghandi was opposed to industrialization, and Ghandi's beliefs still dominate the thoughts of millions of that great country who consider him practically as a saint.

The preceding is a diversion, I must admit, but might help to explain why we found the higher education program of India narrow and traditional in the extreme. It involved a concentration in a very few subjects throughout the entire undergraduate degree curriculum, the student attending lectures and reading in these subjects exclusively. My colleagues and I felt that if we could help infuse the spirit of breadth in the training of the young men and the young women who will have such an important role in facing the staggering problems which India must solve to take her rightful place as one of the great nations of the world, it would be a highly desirable development. We felt also, and felt this very keenly, that it is crucially important to the western world to help India remain a democracy. I came back an apostle for economic aid to India, with no political strings attached, and for educational exchange, and technological assistance, because I believe that the fate of the free world will be determined in large measure by the success or failure of democracy in India.

I would like to return from this brief excursion to southeast Asia to consider the third major factor or type of educational objective which the teacher has a part in realizing. That is in serving his students as a personal guide and advisor. It is undoubtedly often difficult for the teacher in the classroom whose attention is constantly diverted by a variety of personal and professional matters, to realize the full impact of himself or herself as an individual upon the students who are in his classes or with whom he has contact. This was borne in upon me sharply a number of years ago when in conducting a class for prospective college teachers, I asked them at the onset of the course to write a brief essay on the topic, "Why I want to be a teacher". I anticipated somewhat the kind of result I might get from this exercise, and yet I was deeply impressed as I read one after another these brief statements. So many of them ran something like this: "It was because of a teacher in high school whom I admired very much." "It was because in college I had a teacher who inspired me with his point of view about people and about knowledge and about learning." "It was because of a teacher who inspired me with the desire to help others, as he was doing." Or a fairly frequent statement like this: "I had not the faintest idea or plan of becoming a major in history, for example, and yet one of my college professors influenced me so profoundly, although I don't think he knew it, that I have chosen to become, like him, a teacher of history." John Ruskin, has, I think, given voice to this larger challenge to the teaching profession in talking about education in these terms. "You do not educate a man by telling him what he

knows not, but by making him what he was not. Education is a moral experience and so teaching is a moral act. The entire object of a true education is to make people not merely do the right thing, but enjoy the right thing; not merely industrious but to love industry; not merely learned but to love knowledge; not merely pure but to love purity; not merely just, but to hunger and thirst after justice." This is indeed a broad and profound challenge to those of us who have the privilege and opportunity of serving as teachers at any level from Kindergarten to Graduate School.

These larger objectives of nurturing student development beyond the learning of content in terms of facts, and understandings and skills could be, it seems to me, summarized in three individual categories. The first of these is <u>to help the student discover himself</u>. In this connection, I like the anecdote which has been told by Sarah Blanding, at one time president of Vassar College, who was conducting a class of girls who were going to be teachers of young children, trying to impress upon them the necessity of stimulating and of inspiring the youngsters to learn. Finally one young Miss caught on and said brightly, "Oh Miss Blanding, I know now what you're talking about--first you kindle a spark and then you water it carefully".

The second of these broader objectives is <u>to help the student enlarge and mature his own interests</u>. Perhaps we need to remind ourselves occasionally that he is a growing, changing, maturing individual, not an empty and inert receptacle into which we pour the heritage of the past and the fund of knowledge which we ourselves have accumulated. He is a person, a growing person, a different person individually from his fellows. This is the persistent testimony of research in all the behavioral sciences.

Our third objective of this kind is <u>to help the student achieve greater personal and social usefulness</u>. All of us are motivated all our lives by a great urge to be acceptable to our peer groups. It is not the exclusive function of formal education to help people attain this end. Our magazines and newspapers are filled with advertisements which tell the reader how to be happy by doing this, or buying such and such a product, how to be well-adjusted doing that, how to be loved doing something else, and how to be accepted in one or another way. This is part of our heritage, the great gregariousness of the human race, the urgent desire to be accepted and liked by ones'fellows. And we as teachers surely have a part in helping develop this aspect of student life and learning in a constructive and positive way. This responsibility is not one which we can shrug off and say, "Oh, well, we have a student personnel program, that is their job to do." They have a job to do, that is true, the student counseling and guidance staff performs very valuable functions, but no student guidance or personnel program in the world, no matter how good it is, can completely replace the impact of the individual teacher's personality upon his or her students. They can do much, in their own way, but they cannot substitute for us in this respect. It does not necessarily require, on our part, an overwhelming super-salesman, Dale Carnegie type of personality in order to exert a worthwhile personal influence upon our students. I think that Maria Sanford, who was at one time on the staff of this University, has said this very well, not only for this context, but for many others in stating, "I believe men and women would be spurred to far higher development if they were convinced that it is not some special genius conferred upon the few, but the wise use of the gifts common to all that makes life rich and valuable."

In discussing the objectives of higher education and the teachers' role, we are actually concerned with what may in truth be termed the development and conservation of human resources. I should, therefore, like to conclude with an analogy about conservation.

A number of years ago, in an article entitled somewhat dramatically, "Six Inches from Starvation", Fred Bailey stated that one could stand at the foot of Canal Street in New Orleans past which the Mississippi River flows and can see parts of 26 states roll by on the way to the Gulf of Mexico. "Accurate tests have shown", said Mr. Bailey, "that the top soil equivalent of one ten thousand dollar Midwestern or Great Plains farm rolls by the foot of Canal Street every thirty minutes, day after day, year after year". The Mississippi River, he states, and other rivers and streams, have robbed this nation in the past fifty years of more good farm land than still remains in the states of New York, Indiana, and Iowa. The point of his article is that we are now only six inches from starvation, because the topsoil of this nation, which originally measured nine inches in depth, is now only six inches deep, and this topsoil is the ultimate source of all of our food.

We in the college teaching field are dealing with the most precious resources any nation can have--the talent, the character, the personality, the minds of our young people. We are, in a very real way, the conservers of human resources, and these resources, we must agree, are our finest, our best and they constitute our greatest potential as a nation. The teacher may meet in part this grave challenge and responsibility by so designing and implementing the objectives of higher education that they may be achieved as fully as possible by the young people entrusted to our care.

SPECIAL TRAINING OF PROSPECTIVE COLLEGE TEACHERS DURING GRADUATE RESIDENCE

Gordon M. A. Mork

It gives me a great deal of pleasure to be invited to address your conference, and I am honored by the invitation. May I also welcome you most sincerely to Minnesota on the behalf of a sister professional organization, the Minnesota Education Association, of which I am currently the president.

I am especially interested in your attention to the importance of the teaching of your professional field. Only recently I attended the national conference of the National Commission on Teacher Education and Professional Standards of the National Education Association at Bowling Green (Ohio) State University. The emphasis of that conference, sponsored jointly by the NEA with such groups as the American Association for the Advancement of Science, the National Council of Learned Societies and the National Research Council, was on the importance of joint action and mutual effort by the subject matter and the methods people in the production of better prepared teachers for the nation's elementary and secondary schools. You are, in effect, placing a similar emphasis here in one branch of professional education on the college level.

It is indeed gratifying to note the attention that your conference is giving to such topics as evaluation of student performance, challenging the superior student, the objectives of higher education, and criteria for evaluating teachers, in addition to the many splendid and intensive presentations which I know you are having in your own highly specialized field, pharmaceutical chemistry.

My brief remarks today are directed more toward the description of a program which was conducted here at Minnesota and in a number of other colleges and Universities, and in which I participated, than toward discussing what I think might or should be included in a graduate resident training program.

I am referring specifically to a program of college teaching internships which was carried on for three years, in the mid-fifties, in our Graduate School, under the sponsorship and subsidy of the Ford Fund for the Advancement of Education. Similar, though not identical, programs were conducted in about a dozen and a half other colleges for one or more of those years.

A committee of graduate faculty members appointed by Dean T. C. Blegen of our graduate school was the policy-making group for the internship program. It also outlined the procedure for the selection of the students.

For each of the three years a sub-committee of the above policy committee selected about a dozen graduate students to be recipients of the fellowships involved. Represented at different times were faculty members from History, Zoology, Agricultural Economics, the Institute of Technology, English, and Educational Psychology. The policy committee represented even broader participation.

Dr. C. Gilbert Wrenn, professor of educational psychology, was senior co-chairman with me in the administration of the program.

The interns were carefully selected. Applications were solicited campus wide, and eventual selections included people from many different colleges and departments, including Pharmaceutical Chemistry. Selected were those particularly known for having expressed strong desires to be college teachers, and they were required to have finished their preliminary examinations for their doctorates. (In our program this follows the course work and preceeds the dissertation.) It was clearly understood, however, and entered by the interns as a gentlemen's agreement, that they were to be spending their full time as interns, and the program was not designed to subsidize graduate students completing theses:

Each intern was given planned experiences under four major headings. First, he worked under the direction of a sponsoring professor, a major professor in his department, but preferably not his major adviser, for rather obvious reasons. This sponsor played an important part in the program. He had to agree to give of his time and energy to his intern. Response and cooperation from the sponsors was excellent. Under the sponsor the intern planned some teaching in his department, preferably an introductory course and later in the year an advanced course. He observed the teaching of the sponsor and with the sponsor's help arranged to observe other teachers in his own department and elsewhere. The intern also had regularly scheduled conferences with his sponsor who was expected to be his confidant and confessor.

Secondly, the intern was to be accepted as a regular member of the department, given an office, be paid by instructor's salary (supplied by the Fund), and share in the normal responsibilities of a new instructor in a department. In addition it was expected that he would devote some time especially to departmental problems, perhaps the preparation of new syllabi or revision of old, the improvement of examinations, counseling with students, and the like. In this, other major professors than the sponsor might work with the intern.

Thirdly, the intern participated in a weekly seminar set up by the policy committee and conducted by its members, particularly the co-chairman. Many faculty members participated in these seminars, occasionally, but not regularly, the sponsors, other professors by invitation, and the interns themselves. The topics discussed were set partly by the committee and partly by the interns. Topics discussed included the philosophy of higher education, objectives of higher education, current problems in higher education, objectives of the fields of specialization, the organization and administration of a university, classroom techniques of many kinds, the preparation of exams, planning instruction, formal and informal counseling of students, the psychology of learning, the day to day problems of working with students, and many more.

Finally, the interns participated in planned visits to other institutions. They were permitted two trips to other colleges selected with the help of their sponsors, and subject to the approval of the committee. Usually they selected departments known for their outstanding programs and for professional leaders in their fields. The selected colleges ranged all the way from the eastern seaboard to many in the midwest, and several, of course, in the vicinity of the Twin Cities. The interns

were encouraged to interview staff members, observe organization and procedure, to live with students and to discuss informally with students and staff the many phases of college life.

These interns are now widely spread to many positions in higher education throughout the nation. We have made no formal follow-up study, something which we do plan, however. At the end of each year each group was studied, and its reactions to a rather carefully prepared inventory were compared with the responses and reactions of a control group of beginning instructors representing roughly the same colleges and departments in all the participating colleges and universities. The study, conducted by the Fund, was thus rather broad in its scope.

It was found that the interns seemed to differ in some respects from their full-time-beginning-instructor counterparts in their responses to the inventory. The interns seem to have more questions about their roles as teachers, that is, to exhibit a greater awareness of their function. They seemed to indicate somewhat greater awareness of higher education and its problems. They also seemed to be more cognizant of student problems. They clearly felt the need for more actual teaching experience. Further study of these people now would be interesting, casting greater light perhaps on the potential strengths and weaknesses of such internship programs.

Last effects of this program on our own campus are difficult to evaluate. In a few instances the interns have become permanent staff members, but only rarely. Sponsors, and in some instances department chairmen and major professors, have expressed the opinion that working with this program made them more conscious of the needs of the young college teacher. Some have indicated a desire to incorporate formally or informally some aspects of the internship program into their departmental procedures. We have no formal assessment of the extent to which this has been done.

The interest of Dean Blegen in this project and his continual emphasis on quality college teaching, have undoubtedly had an influence throughout our graduate school. The participation of the many major faculty members as committee members, sponsors, seminar participants, and the like has also had some effect, perhaps, but this too is difficult to assess.

For my own part as a committee member, sponsor, and co-chairman of the seminar, I felt there were many outcomes. For one thing, I was impressed as never before (indeed, this gave me a unique opportunity for observation) with the sincere and devoted attention which many of my most respected colleagues pay to their responsibilities as teachers. This is in addition to their scholarly and research interests and activities in their respective fields and disciplines.

In the years ahead such pilot studies as this one may well help us to prepare better our young instructors for the difficult and challenging task of helping us work effectively with the many students and shortages of staff which we know are before us.

DISCUSSION

Dr. Webster wondered what the sponsor should teach the intern about teaching and how this can be done (through seminars, conferences, etc.)

Dr. Mork: "..... there is no one way of teaching which is best ... for all of us. We hear of people who find fault with the lecture method of teaching .... group dynamics, etc. And yet you will find in every one of your departments, on every one of your campuses ... people who are outstandingly successful as lecturers, but not as the leaders of discussion ... others who are outstandingly successful as discussion leaders but are just unable to give a good lecture. We can go through all the other techniques. I think that the sponsor must try ... to assess the potential of the young teacher ... to help him with things that are obviously too weak ... primarily ... to develop his confidence, his interest ... much of this has to come by example ... (and) by individual conference between the sponsor and the young teacher. Some of this is ... soul searching ... when you point out to someone else his strengths and his weaknesses ... at the same time you confess some of these ... about yourself ... I think individual, face-to-face two man conferences are the best way to get some of these things across. Now in the questions about philosophy, the outlook toward higher education, and the role of the college teacher in the whole scheme of things, I like the ... seminar approach. It was interesting to us to watch ... how these young people went to work on each other. Some of them would have very strong ideas ... and they were free to discuss these. There were no course grades ... no credits ... nobody was threatening anyone else at all and they really opened up. It was interesting to watch how from very divergent views ... they usually shifted the dynamics around so that at least their ideas would overlap ... I think this is very difficult to do in a departmental discussion where you are sitting with the professor who is on your committee ... your adviser ... some individual whose work you have followed and admired for years. (Under these circumstances) the intern does not open up, he just tends to sit."

Dr. Webster asked about the advisability of general seminars of this type for groups of graduate students in chemistry or physics.

Dr. Mork agreed that the idea is a good one and pointed out that the key to success would be the prestige factor from having present senior faculty personnel. The enthusiasm and support of the faculty would be necessary for its success.

Dr. Lauter testified to the benefits from a course offered in the College of Education entitled, College Teaching. One is made aware of two deficiencies characteristic of the teacher who lacks training in education, viz; selection of course content and preparation of examinations.

Dr. Mork agreed that such a course is found to be very effective, particularly when presented by outstanding individuals.

A comment was made on the advantages of training of this type for graduate students whether they plan to teach or not. Knowledge of subject matter depends in large measure on the ability to explain it to someone else. Dr. Mork agreed that

such training is important, especially in the case of teaching assistants who often carry part of the instructional load of a busy professor. The opportunity and the need for this type of training impose a serious responsibility on the adviser.

Dr. Webster requested suggestions in regard to selected courses in education that could be especially useful to subject field specialists.

Dr. Mork agreed that the feeling sometimes prevails that all courses in education must be studied in order to profit from selected courses in this area. Persons from other departments are welcomed into certain education courses, e.g. the College Teaching course mentioned previously, Psychology of learning, building of tests, educational philosophy. "... I would hold myself, and I think most of my colleagues do, very strongly for an open-door policy, for people in other subject matter departments who want to improve as teachers, ... to come over and just take a course or two without having to run the entire gamut of courses."

Dr. Martin told of a course in which the various topics in the lecture outline were presented by the students themselves. The procedure proved inspiring to the students and worked out quite well.

Dr. Mork agreed that this is an excellent program and one in which subject matter becomes more understandable through the necessity of explaining it to others.

THE TEACHER AS A RESEARCH DIRECTOR

Maurice L. Moore

Dr. Webster, ladies and gentlemen --

It is a pleasure indeed to be with you here in Minnesota today and participate in the American Association of Colleges of Pharmacy Teachers' Seminar on Pharmaceutical Chemistry. I have so many personal friends among you that I am delighted with any excuse which permits me to talk and visit with you. (Comment on the weather in Minnesota.)

I have been asked to discuss "The Teacher as a Research Director." When Dean Hager asked me to take on this assignment, I wasn't sure whether he assumed I was a Research Director and could intelligently contribute to a discussion of this subject, or whether he just wanted to find out -- after preparing this manuscript, I am still not sure. I don't believe that you can tell anyone, especially a professor, how to conduct research, but perhaps we can discuss the problems and techniques of research programming and activities. When I talk about research in this discussion, I refer particularly to my experiences and problems in pharmaceutical and medicinal research, i.e., scientific research activities in the health field.

Before discussing the teacher as a Research Director, let's briefly review and consider the teacher as a teacher. An understanding and evaluation of this responsibility might help us in our approach to the other phase.

A teacher has the responsibility of presenting facts, theories, information and knowledge in his particular area of specialization and competence by means of lectures, talks, demonstrations, etc. However, as important as is the presentation of this factual information, the teacher has a much greater obligation. To be effective as a truly great teacher, he must be an arouser of interest, a stimulator of ideas, a developer of understanding and the ability to think, a creator of wisdom, a cultivator of judgment and a translator into constructive, beneficial and productive action.

The teacher should provide the student with certain kinds of abilities of which every man is the better for possession:

1. The most important of these is variously described as "the ability to think clearly," "rigorous thought," "intellectual discipline," etc;

2. Another is the ability to find out information and knowledge for himself -- not just what is given to him by his teacher or from his textbooks, but from other sources that are available to him;

3. Thirdly, the ability to understand what he has found out, form judgments of value on the basis of this knowledge, and to translate this into constructive action; and

4. Finally, the ability to express and convey by spoken or written word his thoughts and ideas to others.

If a teacher is in reality all of these things, he is already well on his way to being a good Research Director.

As a Research Director, what are the responsibilities in the scope of the teacher? First and foremost, he still has the responsibility of teaching. In other words, his primary responsibility is to train potential research investigators and future Research Directors in the techniques of scientific method and inquiry. Thus, his primary concern should be in the student. What is needed to give the student the best training, background and experience in conducting research investigations? The teacher must kindle the spark of scientific interest and curiosity, develop the student's abilities and ground him in the techniques of scientific procedures. To do this effectively, he must be able to plan and carry out a constructive research program with the active participation of his students. One can teach a person to pursue research by showing and doing as well as by telling.

Secondly, it is acknowledged that the teacher has a responsibility to increase and advance the store of basic knowledge in his field of specialization. The discharge of this responsibility can also be used to arouse the interest and enthusiasm of the student for research work.

While it is admittedly difficult to tell one how to conduct research successfully, there is some orderliness in organizing a research program which can be taught to properly motivated students. This is very important because the majority of graduate students will go into industrial research laboratories, where they will be confronted many times with new problems distinctly different from those that they have worked on, so that the techniques of tackling and effectively handling strange problems becomes an important factor in their future success as research leaders.

What are the steps or phases in the development of a successful research program? From my own experience in industrial and academic laboratories, I think the following merit attention and consideration:

1. Planning --

   Students should be made aware that effective research programs and projects do not emerge spontaneously. There must be a planning stage when thoughtful attention is given to the question of where one wants to go in his research efforts. This is equally true whether it is a company or individual developing the research program. What kind of research do you want to do? What fields are you interested in investigating or justified in undertaking? The criteria for these decisions differ for the individual and for an industrial company; but such decisions are equally important to both for the success of their program. Each must define the fields that should be studied and the emphasis to be placed on the various kinds of research activities in each field.

   Pharmaceutical Fields:

   Cancer Research -- Common Cold -- Pharmaceutical Development -- Synthetic Medicinal Drugs.

2. Objectives --

When the fields have been set up, we must clearly define the objectives which we want to achieve in the program or projects. Just what is wanted from our research efforts? Why are we trying to achieve these objectives? There must be valid reasons which can be understood and appreciated.

Common Cold Field:

a. Etiology -- Are we interested in establishing the cause of the Common Cold, isolating or identifying the causative agents, etc?

b. Chemotherapy -- Perhaps we are more interested in evaluating old or new compounds for activity against various cold symtoms and conditions; or,

c. A Cold Cure -- Perhaps we are interested in developing a cure for the Common Cold -- undertaking the synthesis and development of some new compounds or products for this purpose. At this stage, we may not know what the compounds are, but we should know what we want them to do if we are able to obtain them.

3. Formulation of the Problems -- Project Selection --

Having set down the objectives, it is necessary to spell out the problems anticipated in achieving them. The real problem must be clearly understood with its environment and its true limitations.

In the field of --

Cancer Chemotherapy --

Maybe the real problem is the lack of an adequate method for testing anticancer agents. This would then become our actual research project; or we may have a good testing method, but no active compounds or agents have been discovered so that we must undertake a broad screening program; or we might have some active compounds, but they are too toxic for human use. Our problem is to try to eliminate toxicity and retain activity by modifying the structure.

Penicillin Synthsis --

The problem in the synthesis of penicillin may be just one step in a multiple step procedure. All of the others may involve established workable reactions, whereas one or more steps may involve the modification or adaptation of known reactions, or the development of new ones. Under these conditions, our project is concerned with the solution and completion of this step.

Product (Formula) Incompatibility --

In our industrial pharmaceutical laboratories, we have many problems concerned with the incompatibility of various active ingredients, parti-

cularly in connection with our new compounds. The problem here is to find out which ingredients are really involved in the incompatibility; it may be simply a chemical reaction between two of them.

The successful formulation of the problem, focusing attention on the real difficulties, is one important key to successful research effort.

4. Preparation of the Problem --

Before undertaking a solution of the problem, it is desirable to obtain all existing knowledge bearing on the problem at hand. Search the literature -- consult all specialists and authorities in the field -- learn all that is known about it.

5. Solutions to the Problem --

Search for and consider all conceivable ideas for solutions to the problem no matter how fantastic or absurd they seem. Rearrange ideas, imagine further data, mentally construct possible solutions before setting out on any experimental work. Completely immerse oneself in the question of possible solutions to the problem. Here is where brainstorming techniques have proved helpful and where the idea ability of the genius shows forth.

Creativity -- Idea Ability -- Imagination.

6. Design the Investigation --

The technical feasibility of all alternative solutions available is assessed and the highest analytical ability and judgment is exercised in selecting the "right solution" to follow up or "right approach" to pursue. One tries to establish the best possible solution desirable for the purpose.

7. Carry out the Investigation --

The highest technical skills possible are cultivated in order to carry out the procedures necessary for the solution in a practical way. Careful and precise experimental manipulations can sometimes determine the success or failure of the project, but in all cases contributes to the quality of the results obtained.

Let me not underestimate the importance of technical procedures and techniques, but let me remind you that it is the seventh item in my list and that six others come first. These first six all require real brain power before we get to man power. I mention this because, all too frequently, many of our young technical graduates are all fired up to get into the laboratory and get started on the mechanical part of a project before they have done a thorough job on the mental part. (Have you ever noticed how often when you ask a young researcher: "How are you getting along with your project?" the first thing he tells

you about are the mechanical manipulations and operations he has carried out. Seldom does he tell you about the thought, if any, he has given to it.) This fault, if not corrected, soon creates a ceiling on the potentialities of the individual. He tends to become what we refer to as a good "bench technologist" rather than an outstanding "creative scientist."

Doing the work to see where it leads us does pay off sometimes, but the odds are heavily weighted against it.

Fortunately for most, the next step forces most of us to go back and do a more thorough planning job.

8. Re-Evaluation of the Problem --

As each step in the actual experimental work is completed, we must evaluate the data obtained, interpret the results and establish the significance of the findings to provide guidance and direction for further experimentation until the desired solution is obtained or the idea is abandoned. The investigator should continually test his ideas and results against the knowledge, experience and judgment of himself and others to make the necessary modifications or alterations in the program for the successful accomplishment of the objectives.

We must remember that scientists do not always apply cool and dispassionate judgment to their work. Pride of authorship can be very strong indeed. Ideas are like children -- they are wonderful when they are your own. Thus, a successful research investigator must continuously re-evaluate his ideas and plans for his research program.

At this point, I think it is appropriate to point out that some of the most important discoveries in our field have come about from the ability of the investigator to recognize the significance of some unexpected result or finding, in the course of a scientific problem, which offers the possibility of solution for another equally important problem. Serendipity plays an important role in pharmaceutical and medicinal research. Here, an awareness and understanding of the various problems in a given field enable one to achieve greater results from one's efforts. As an example, when I was working on the sulfonamides, we were trying to develop a group of compounds having a sulfathiazole activity with longer duration of action. In trying to achieve this objective, we were making a series of acyl derivatives of sulfathiazole which would give a prolongation of blood levels in the animals, but at lower levels than those desired for effective antibacterial action. We were then trying to step up the absorption and concentration of these compounds in the blood stream by increasing their solubility through the preparation of dicarboxylic acid derivatives which were found to be much more soluble. Imagine our surprise when we were not able to obtain any of these compounds in the blood stream! After establishing this fact, we were led to

investigate their use as antibacterial agents against infections in the intestinal tract, out of which came Sulfasuxidine and Sulfathalidine.

9. Communicate the Problem --

Whether it is preparing the initial comprehensive proposal for the over-all project, including the information in the first six steps outlined above, or reporting the ideas and results achieved during the course of the project under 7 and 8, or preparing the final report and results for management evaluation or subsequent publication, it is important to communicate the information obtained from the project for use by others. A research project is not completed until the results are recorded as a paper, a publication in a scientific journal, a Patent Application, a company report, etc. In industrial research, we hopefully look for a new product which can be marketed as a reward for the expenditure of our effort and money, in addition to the final project report.

If the above steps or phases are important in the development of a successful research program or project, what are the desirable attributes and qualifications to be developed and cultivated in a prospective research investigator in order that he may carry these out most effectively? Many articles have been written on this question, and a long list can be prepared, but I think the following, some of which have appeared on other lists, are among the more important:

1. Scientific Curiosity --

A student should have an insatiable desire to explore new areas in his field, constantly seeking new knowledge and striving to uncover some new information in order to become better informed.

2. Creativeness --

The ability to synthesize, create, or conceive significant ideas that are pertinent to the problem at hand is one of the most important attributes of a successful research investigator. Idea ability, including both quality and quantity, cannot be underestimated even though it is one of the most difficult to evaluate. We are all looking for the really good idea man, and we sure try to hang on to one when we get him.

3. Productivity --

The ability to achieve results is another important attribute -- not just turning out so much work (most people can do this -- few of us are really lazy), but the actual production of significant results which have meaning and usefulness for those working in the field.

4. Training and Ability --

Broad, basic background knowledge and training in science are very important as a foundation for development. The wider one's knowledge,

the greater opportunity for success. However, all the knowledge in the world doesn't make one a good research leader if he is unable to use it effectively. Initiative, drive and ability to think are prerequisites for good productive research.

The next attribute I want to mention is:

5. Personality -- the Ability to Work Well with Others --

Today, most of our research problems are so complex and diverse that many different scientists and disciplines must be utilized in their solution. Thus, a scientist may find himself working with a number of assistants; a group of associates in his own or related fields; and on occasion, under the direction of others. The effective solution of the problem may well depend upon his ability to get along with these people. Certainly, his potential with an industrial organization will be influenced by this ability.

A few lone workers still remain in our laboratories today, but even in the university, the successful direction of graduate research programs requires a teacher who can get along with his students and other faculty members and train his students to work efficiently with others.

6. Ability to Organize the Problem and Himself --

Having these complex and diverse problems to solve as mentioned above, the leader of the group emerges as the individual who is best able to tie together all of the various elements and organize the project effectively, including that portion which he must carry out himself. Organizing and carrying out the program efficiently and expeditiously in regard to time and money becomes important for success because of the competition -- professional, as well as industrial. If the project takes too long, someone else may solve it first, in which case, one ends up by confirming the work and results of others.

7. Honesty and Reliability --

In scientific research, one must be able to rely upon the accuracy and honesty of the investigator. It is impractical to verify all of the technical work being done by an individual in order to be sure of his findings. Dishonesty and unreliability are serious offences which cannot be tolerated.

The last quality I want to mention is the:

8. Ability to Communicate --

Writing and speaking well are essential requirements for the scientist. He must constantly present and explain his ideas, work and results to others. Many times this involves people who are not versed in his own field and speak a different language. Today,

the scientist has the responsibility of bridging this barrier and making himself and his work understood by the non-specialist.

Having outlined what I believe are important steps in the programming of research and the desirable qualifications of a successful Research Director, we come to the question of: "How does the teacher as a Research Director educate his students in the essential mechanics of planning, organizing and conducting scientific investigations and cultivate those attributes which we insist are so desirable?"

You are more able to suggest answers to this question than I. The answers will vary according to the abilities and temperaments of the individual teacher. However, I think you will agree that the problem is to find methods and techniques which will stimulate, challenge and hold students to a high standard of excellence in their performance, at the same time providing satisfaction and a sense of accomplishment for them. A reminder of some of the possible ways of achieving the desired results may lead us into a more productive informal discussion later:

1. Selection of Problems --

   Some teachers maylike to assign problems directly to each student on the basis of his interests and abilities. Others may prefer to assign a number of productive problems so that discouragement on one hand is offset by success on the other. The student may find one of them at least that stimulates his interest and elicits original suggestions. Other teachers may allow the student to select his own problems. I think it is usually desirable to suggest ideas and possibilities for problems to the students and ask them to suggest others, but leave the actual choice up to the student, with guidance by the teacher on the evaluation of why and how. Make the student think through all the steps in selection and provide a rationale for his choice.
   (Add item from Booz, Allen and Hamilton booklet, page 13.)

2. Library Work --

   How many of you insist on thorough library work before the problem is decided or planned out? Are you sure that the student has received adequate training in literature searching and the effective use of journals? Do you emphasize the importance of continuously keeping up in the field? Do you check your students' scientific reading by questioning them on current articles which you have noted? Shouldn't you insist that the student read more on the problem than you?

3. Outline of Project --

   Do you require the preparation of a precise and concise write-up of the project before the student gets under way with it, such a write-up to include the following items among any others which you might want?

a. Objectives.
b. Problems anticipated
c. Outline of alternative solutions considered, with an indication of the advantages and disadvantages of each.
d. Lines of investigation to be pursued and why.
e. Results sought

It is important that the student learn to use his head on his research problem before he starts using his hands.

4. Direction of Project --

Some teachers may want to exercise close supervision of the technical work. Others may leave it up to the student to proceed on his own and to come in for advice and consultation only when he runs into difficulties. Here again, I think it might be desirable to schedule conferences on the work at regular intervals when the teacher would ask questions, stimulate ideas and evaluations on the part of the student and not just give directions or suggestions. This is the time and place when the student can be stimulated to develop his own ideas and check them against the knowledge, experience and judgment of yourself and other faculty members and graduate students. How many teachers suggest that their graduate students discuss their own ideas for the research problem with other members of the faculty?

In industry, we have found it necessary to insist that our creative research scientists consult with others in the company and with outside consultants and specialists. We try to challenge our ideas and plans at all levels to obtain the highest standard of performance, understanding and judgment.

5. Reports --

Some teachers require weekly, monthly or quarterly reports. Others require reports only when there is something significant to disclose, or upon the completion of specific phases of the work. All usually request a full and final report upon the completion of the problem. Reports should be considered as a means of communicating ideas, thoughts and results on research problems to the appropriate people interested in them, whether in academic or industrial circles. Again, I believe that reports should be expected at reasonable intervals, but they should be used to reflect brain power, judgment and results -- not just status. The whys of certain things being done, the meaning of the results obtained and the reasons for doing additional things in the future are the points which should be covered in reports.

At Vick, we require a comprehensive project proposal, which goes to the Vice-President for Research and the President of each Operating Division, before a project is put on our official research slate. We then have a brief summary status report on each project every two months. The project director prepares the draft, which is included in an over-all laboratory report prepared by the laboratory director. The

laboratory report goes to the key executives of the company. As various phases of the project are completed, an interim report is prepared on it, or as new leads or ideas are developed these are reported for evaluation and consideration by certain officials before becoming a part of a major research project. As most of our work ends up with a new product, we prepare a number of technical reports, such as:

1. A technical facts report on the product is prepared for use by the clinicians in their study on it.

2. A Patent Application is prepared on all patentable ideas and inventions.

3. A New Drug Application is prepared when needed on completion of the technical and clinical work.

4. A new products brochure is prepared for consideration by management in making their decision to market or not market the product.

Thus, the preparation and use of constructive reports is an important part of the research investigator's tools. The better and more understandable the report, whether a paper, Patent Application or internal company report, the better one's work will be understood and appreciated.

Conclusions:

Outstanding research work is the result of creative ideas, careful planning and organization, skilled experimentation, sound judgment and hard work on the part of our research leaders. There is a necessary orderliness in organizing and carrying on a research program for most effective results, including:

1. Planning.
2. Stating the objectives.
3. Formulation of the problem.
4. Preparation of the problem.
5. Solutions to the problem.
6. Designing of the investigation.
7. Carrying out of the investigation.
8. Re-evaluation of the problem.
9. Communication of the results.

Among the necessary attributes for an individual to carry out this program most effectively are:

1. Scientific curiosity.
2. Creativeness.
3. Productivity.
4. Training and ability.
5. Personality.
6. Ability to organize a problem.
7. Honesty and reliability.
8. Ability to communicate.

Stimulating teachers working closely with their students on specific research problems as a means of training them as investigators capable of tackling any research problem in their field, have the responsibility of providing our industrial and academic institutions with potentially outstanding research leaders. The quality of mind power with initiative, drive and ability to think and follow through are of primary importance in our research effort and will provide the means of answering our most difficult technical problems if these are marshalled in an orderly attack upon them.

The demand for such research leaders in the health field will be even greater in the next few years. The pharmaceutical industry is spending over $125,000,000 on research now, and its budget is growing each year. The Senate has just raised the budget of the National Institutes of Health over $115,000,000 to a total of about $360,000,000 for 1958-59. This marked increase in research expenditures will create a demand for more and better qualified research investigators.

I hope these remarks have stimulated you to initiate a more detailed discussion of those aspects which are of greatest interest to you.

DISCUSSION

Dr. Webster questioned the speaker on the proper procedure for selection of problems by graduate students.

Dr. Moore pointed out that the selection of problems would vary according to local situations. In any case the "initiative abilities" of the students must be developed. The teacher is remiss if the student is not challenged and "expected to come up with something themselves in the way of ideas." Skilled technicians are needed, yet the teacher's greatest responsibility is the development of creative scientists. "If you have all the ideas and he works on those for you, he may become a real skilled craftsman, but he won't be challenged as much as he might be in his idea ability."

Dr. Smissman raised the question of industry's practice in assignment of problems.

Dr. Moore stated that in some cases personnel is hired to do specific jobs, for expansion of existing programs, etc., yet such persons are expected eventually to undertake work in new programs in other areas. ".... I suggested that you give ideas and suggestions to the student, but also challenge him to come up with ideas and suggestions and, with your guidance, make a selection .... (It is) most important to make him go through the selection steps even if he ends up by selecting the one you got him to select."

Dr. Smissman raised the question of emphasis on basic research or applied research in an academic locus. In the ensuing discussion there appeared to be agreement that basic research thrives better in an academic atmosphere while applied research is better conducted by industry, although there is a growing activity in basic research in industry. More industrial support of basic research in colleges of pharmacy was recommended and an appeal was made for better understanding by industry of the training of pharmaceutical scientists in colleges of pharmacy.

CRITERIA FOR TEACHER EVALUATION

Melvin W. Green

Possibly history will record that the year 1958 was the year when Americans exhibited dissatisfaction with two of their most cherished possessions - their automobiles and their schools. No doubt some of the chrome will come off both, but it is to be hoped that the American people will ask the important question - what are automobiles and schools for?

We are in the midst of a period of the critical evaluation of the entire educational milieu from the kindergarden to the Ph.D. Many believe that it is fortunate that this rekindled interest in education comes at a time when the primary and secondary schools are feeling the full pinch of Malthus and colleges and universities are trying to gird themselves for the battle of numbers. If ever there was a time to haul out the educational microscopes, spectroscopes, and the Univacs to evaluate where we have been, where we are and where we are going - this is it.

There is no phase of higher education that does not need critical evaluation today. The philosophy of higher education in relation to the society it is expected to serve, the mechanics of teaching, academic bookkeeping, curriculum planning, bricks and mortar - all of these things and more need attention, and I might say are getting attention at least within the limits imposed by the criticalness of the times.

The evaluation of many of these parts of the education complex is not too difficult. It should not be hard to evaluate the space available for the teaching programs at hand and the space needs for the future, for example. It may be more difficult to arrange to meet these needs. Teaching loads, faculty salaries, grade distributions, admission standards and similar elements lend themselves to rather easy study by the statisticians tools. But it is my poor fortune to have drawn the assignment of discussing the criteria for evaluation of the teacher, the most difficult of all evaluations to make.

I have seen more teaching and talked to more teachers than nearly anyone in this room. I have seen excellent teaching and I have seen miserable teaching and, yet, I hesitate to come before you and try to define a good teacher. Why is this the case? For one thing, I am reminded that someone has said that nothing a teacher does is alien to his job. This is true of very few workers or professional people and it implies that the whole man or woman must be taken into account when evaluating the teacher. This means that personality is important, but it is not superficial personality as when one evaluates the personality of a receptionist that is to be measured but rather looking deeper into the well-springs of the personality that we call character.

Perhaps another source of difficulty is the learning process itself. Teaching is to cause to learn. Certain facts, ideas, and materials are brought together in the student's mind and he does or does not learn. The teacher is the intermediary in this process and he functions in many respects like a catalyst. It has been only a few years that we have known much about a catalyst in the physical world so it is not surprising that we know little about an educational catalyst. If teaching is to cause to learn, who is the teacher?

Is it always the person that we call the teacher or is it a fellow student, an administrator, a practitioner of the student's chosen profession or vocation, the football coach, a parent, a brother, a housemother, the motorman on the bus, the author of a book. Who is the teacher?

In attempting to write this paper, I was confronted, also, with the question of who is the evaluator? The student, an administrator, a colleague? The outlook of the evaluator makes a difference. I have seen teachers that I thought were better than average in the art. But student John does not think well of him because he gave him a C when he thinks he should have had a B and student Mary remembers that he once belittled her in class. His colleagues do not think so well of him because he is not very cooperative on committees. His dean is annoyed because he is always asking for something. The Dean of Faculties points out that he has never published a paper.

Another reason I find this paper hard to write is the fact that Dr. Deno has already written it. Dr. Deno's paper at the Storrs conference in 1954 covered the literature on the subject then current and there has been little of consequence added to it since. I commend the rereading of Dr. Deno's paper to you, for he has covered the subject far better than I.

How does one determine the efficiency of any worker? A study of personnel management literature would indicate that such determination is made by (1) ascertaining what the worker is supposed to do (2) establishing standards of performance for these tasks and (3) measuring individuals against these standards.

What does a teacher do? He teaches, that is he is the catalyst or at least one of the catalysts that supposedly causes the student to learn. But he does not just teach, period, rather he teaches philosophy, mathematics, pharmaceutical chemistry or whatever the case may be. It is more accurate to say that he teaches students something about one or more of these specialized subjects. This brings us immediately to two arms of the problem - criteria for his ability to teach and criteria for his ability to teach in a given field. In the one case we would be measuring pedagogical skills, in the other, scholarship.

To evaluate pedagogical skills we might examine some of the evidence for his classroom preparation. One could look at course syllabi, lesson plans, teaching aids, class assignments, visual and audio aids, library assignments, examination questions and the like to see how these compare with what are considered well planned and well developed teaching devices.

To witness classroom performance we could visit classes, or more ideally arrange to have the class conducted in a room with one-way mirrors and some sort of listening device. In thus observing the teacher there would be certain things to look for and listen for. We might list some of these observation points: (1) number of different students who recite, ask questions or otherwise participate and the number of students who raise hands or give other evidence of wishing to participate (2) the ratio of participation during the first and second halves of the class period, (3) manifestations of student interest by counting the number of instances where individual students go to sleep, yawn prodigiously, read newspapers or play tic-tat-toe, (4) manifestations of open hostility to the teacher i.e. derisive laughter at the

teacher's expense, mumbling of mutinous comments, etc., (5) evidence of students being unable to hear the teacher, (6) manifestations of annoying mannerisms of the teacher such as meaningless repetitions, failures to finish a sentence, "hemming and hawing", standing in front of what has been written on the blackboard, and dictating material already at hand in a useable fashion.

While the observer can see and hear many of these things for himself, he can get a fairly accurate picture, as far as evaluation of pedagogy is concerned, by going to the student as well. Socrates noted in his Politics, that we get a better notion of the merits of the dinner from the dinner guests than from the cook.

Some notion of comparison between supposedly trained observers' evaluations and those of students can be gained from the case studies cited by Allport.

Over-all Evaluation of Instructors A, B, C, D, E,

Rank Order	By Student	By Observers
1 (Best)	A	C
2	B	B
3	C	A
4	D	E
5 (Poorest)	E	D

"There is agreement that A, B and C are good and that D and E are poor. The reversal of the positions for D and E will not concern us. The reversals of A and C is more serious. We can best obtain light on the discrepancy by presenting abbreviated case studies of these two instructors, the one rated best by the students and the one rated best by the observers.

"Instructor A (observers view): This instructor is both lively and relaxed in manner. He often speaks while pacing up and down with both hands in his pockets, pipe dangling from his mouth, or he straddles the back of a chair or puts his feet on an adjacent support. He talks rapidly, his voice sometimes sinking so low as to be almost inaudible. His manner is modest, and his remarks often apologetic. While class discussion is in progress he sometimes looks up a point in the textbook, a habit that usually gives the impression of insecurity and withdrawing.

"Yet in spite of his apparent lack of poise - or possibly because of it - he seems to be in excellent rapport with his class - to be 'one of the boys'. He looks young; a stranger entering the classroom would have difficulty distinguishing the teacher from the pupil. His manner is totally 'permissive'. A student feels free to say anything - and does so. The class is animated at all times, and sometimes nearly every hand is simultaneously waving in the air. The result is a confused cross-current of ideas, not well controlled by Mr. A. Characteristically he will allow the class to ramble in all directions, and then engage in a rather long stretch of 'lecturing' in order to expound some concept that has eluded the free-for-all discussion. Sometimes he introduces the names of authors or expounds ideas at too advanced a level to be grasped by the class. On the whole he does not seem to be entirely familiar with the subject matter and promises to 'look up' points that he cannot handle in class.

"All the while a markedly friendly atmosphere pervades his teaching. He uses first names of the students, an unusual custom in the college, and issues a sincere invitation to the students to consult him during his office hours - which they take advantage of. Further, he employs undergraduate humor in a wholly authentic manner - again seeming to be 'one of the boys' in this important respect: Social distance between himself and the class is zero.

"Instructor A (students'view): Nearly every member of the class, when asked to comment on A's style of teaching, wrote friendly, helpful, informal, democratic, stressing student participation. Favorably mentioned also were his use of office hours, his humor, his modesty, his willingness to find out what he doesn't know. A few commented on his seeming ill at ease, his halting manner of speech, and his too low voice.

"Since the students definitely like A, they readily excused the faults that seemed to the observers more serious. For example, the lack of planning, organization and control of class discussions, noted by the observers, were 'perceived' by many students to result from 'lack of time to cover the ground'. This extenuating perception is especially interesting in view of the criticism made of less popular teachers who were often accused of 'using the time badly'. Approximately half of A's students spoke of 'lack of time', whereas this protective statement seldom appeared in the protocols from other sections. Thus is a popular teacher readily excused for his shortcomings.

"Instructor C (observers' view): Unlike Instructor A, this teacher establishes considerable social distance between himself and the class. Of the five teachers, he is the only one who places a table or desk between himself and the class while conducting sections. His manner is brisk and business like. The agenda for the day are well outlined on the board and in his own mind. He is explicit concerning every detail: in calling the roll, in advising students whether or not to take notes during the hour, in directing students with unsatisfactory grades to call on him during his office hours. Much of the time he reminds one of an army drill sergeant.

"Yet unlike the proverbial drill sergeant, C is courteous. He tells students not to trouble to raise hands, but to speak freely: 'Break in anytime you want to ask a question'. 'Excuse me for interrupting you'. He also uses students' first names but not as often or as consistently as does Instructor A.

"Mr. C. is a master of the subject matter of the course, and keeps closely to the material presented in lectures and textbooks. He summarizes pertinently and frequently. Occasionally he 'lectures', in a more assured manner than A, indicating explicitly what he plans to discuss, how he proposes to approach the topic, and where his material comes from.

"On the whole, he shows a strong style of leadership, oddly mixed with moments of apology, with colloquial and slang expressions inconsistent with his usual dignity and distance of manner. His voice is forceful and his speech fluent, although he tends to talk too rapidly and too loudly.

"Instructor C (students' view): More than half the students commented favorably upon the organized approach characteristic of C's teaching: they praised his good agenda, good planning, good control of section meetings. Others remarked upon the

freedom in discussion, on the lively, energetic, personable manner of C. One or two saw virtue in his varied style of approach.

"But it is clear that this varied style troubled many students. They could not interpret what to them were inconsistencies in his manner. Why was he both formal and informal, slangy and pedantic? Some suggested that he was not sure of himself, some that he was too sure of himself. One thought that he was trying hard - perhaps too hard. He was criticized for being to explicit concerning points already clear to the student.

"Contradicting the observer's judgment, some students criticized C for his failure to coordinate the lectures, reading, and section work. Yet to the observers 'coordination' was one of C's strong points. We may be dealing here with the tendency of students to cast about for some 'respectable' reason for their vague dissatisfaction. Or perhaps the observers are at fault in overestimating the didactic success of C's efforts at coordination.

"The most striking fact that emerges from a comparison of these cases is that students and 'experts' judge overall value of teaching on different bases. The students seem to favor the section conducted in an informal, friendly, permissive equaliterian manner by a teacher who is authentically one of the boys - modest and humorous. They sense A's keen interest in individual members of the class and his eagerness to help them in any way he can. The 'experts' see greater value in sections conducted more after the fashion of a drill, marked by good organization, with adequate coverage of the ground. Students were obviously disturbed by the inconsistency in C's style. They did not know just where they stood with him. It may well turn out that consistency is an essential attribute of really good teaching. It may not matter whether the instructor is formal or informal in manner, so long as he maintains the role he has once established - that is, so long as he appears to the student to be himself.

"Readers of these sketches may detect in both instructors evidence of personal insecurity. It would not be surprising for both are virtual beginners at the game of teaching. But note the different ways in which A and C handled their subjective insecurity. Instructor A is ill at ease in a 'winning' manner. The students sympathize with him; he is just like themselves in his discomfort (they seem to think). Instructor C perhaps tends to overcompensate, to protect himself, to overexert. Although from the observers' point of view C's effort leads to effective teaching, students are in some cases alienated by his manner, even while they appreciate his ability."

I suppose students have evaluated teachers since time immemorial. Of recent years attempts have been made for systematic student evaluation in different institutions using different methods.

A study by Riley et al of Rutgers University lists the following attributes of teachers for such a study: organization of subject matter, speaking ability, ability to explain, encouragement to think, attitude towards students, knowledge of subject, attitude toward subject, fairness in examinations, tolerance to disagreement, and instructor as a "human being". The Purdue Rating Scale, as developed by Professor Remmers, contains the following items: interest in subject, sympathetic attitude toward the student, fairness in grading, liberal and progressive attitude, presentation

of subject matter, sense of proportion and humor, self-reliance and confidence, personal peculiarities, personal appearance, and stimulating intellectual curiosity. In each of these cases, a scale of values is given for students to check against. For example, under "speaking ability" are given the following four choices "a. Skilled in presenting material, voice and presence excellent, b. adequate, does not detract from the course, c. poor speaker, detracts from the course, and d. poor speaking techniques serious handicap in course."

By using large numbers of students one can obtain fairly reliable results since many of the biases and prejudices as well as insensitiveness of individual students are supposedly diluted out.

The University of Washington has had experience with student evaluation since 1924. By careful and scientific analyses of results they have concluded that such judgments are consistent. They have shown that underclassmen and graduate students tend strongly to agree in their over-all evaluations of teaching effectiveness. Students do not tend to agree as well with the teachers' colleagues however. The Washington studies tend to show that colleagues evaluations emphasize the teacher's readiness to work with others in the department in arranging schedules, examinations and the mass of operational detail, the value of the teacher to the community and the state, and his general knowledge and range of interest. These studies show, also, that class size, grades of students, and the student's major field of interest do not materially effect the value-judgments. In short, there are many aspects of the teacher that can be evaluated by students meaningfully if not effectively. Nevertheless there are other attributes that can be evaluated best by colleagues or even the teacher himself.

When we pass from the merely pedagogical area to teaching in a given field, we are entering the area of scholarship. This is an area that must be judged principally by a man's colleagues both within and without the institution. Generally, the student is qualified to measure this area only to a limited degree.

Scholarship is the distinctive instrument of the university's contribution to the common life. It may be defined as the discovery, organization, interpretation, and dissemination of knowledge.

It is generally recognized that research is a primary responsibility of a university teacher and that the university teacher, at least to some extent, should be teaching things that he learned independently. Moreover the interpretation must be his own. The proportion of research, the percentage of information independently arrived at will, of course, vary according to the nature of the courses taught, but the university teacher is always something more - and something other - than a skilled pedagogue.

First hand experience with the subject matter, which is obviously essential at the post-graduate level and for cooperation with colleagues, is also necessary for teaching at the elementary level. If a university teacher is not a scholarly teacher, even the most elementary student is cheated, for he receives merely facts and not that enthusiasm to interpret facts, and that capacity to acquire more and fresh facts which it is the aim of a university to develop. This is why many departments assign their best scholar-teachers to teach the most elementary courses.

A Scholar is something more than a researcher; for insofar as a researcher fails to disseminate his knowledge, he becomes an expensive luxury. New knowledge, better organization of knowledge, more illuminating interpretation of knowledge, all effectively disseminated - these are the tokens of scholarship. The disseminating phase may involve lecturing in courses, guidance of research students, conduct of seminars, discussion with students and colleagues, presentation of papers and discussion at professional meetings, and publication of books, research papers and reviews.

When the persons who are exposed to a man's influence, whether they are undergraduates, incipient scholars, or colleagues are stimulated by his originality and independence to think for themselves, and to attempt to do things which are new to them, then it is clear that he is a scholar and doing a scholar's work.

The evidence of a man's scholarly qualities may be found, then, in the scholarly characteristics of his published work, the scholarly attributes of his teaching, the influence of his scholarly collaboration with colleagues and advanced students, his success in bringing his knowledge and research skill to bear in applied problems especially within his field and his public services based upon his scholarly attainments.

When the results of a man's labors have been published, they can be examined and weighed apart from personal considerations not only locally but on a national or even international basis. The belief on the part of many faculty members that administrative decisions rest almost solely upon publication as a proof of scholarship sometimes leads to emphasis upon quantity at the expense of quality of publication. Sometimes this leads to piece-meal publication when longer and more coordinated publication would be preferable. This may even lead a scholar to undertake minor research endeavors rather than major ones in order to publish sooner. Often there should be a more conscious effort to encourage the prolonged study.

The dean who encourages such a prolonged study must recognize that he is giving himself the challenging task of trying to evaluate work in progress when that progress is slow and completion of the work must be deferred for a long period. Years may be spent in reading, cataloging, indexing, mulling over evidence and interpreting and reinterpreting a complex situation. How can you tell whether the work in progress is a big undertaking needing, say a half of a lifetime for completion, or a doubtful enterprise that has bogged down or, as happens more often, something between these extremes. This is a problem more acute, I should think, in the humanities than in pharmaceutical chemistry, but it can be significant here too.

When one considers the many diversified duties imposed upon the faculty - remember, nothing a teacher does is alien to his job - a single yardstick of performance cannot be used for all. It is, however, both fair and wise to insist on continued study and high quality work within the field on the part of every staff member, especially in a professional school.

Invitations to review his own and other scholars' work, to teach at other institutions, to give lectures before professional and public groups, to serve in various advisory and consultative capacities, to take part in symposia or research projects, and elections to membership and office in learned societies are all evidences of scholarship. If it is

important to recognize quality in publication it is also important to differentiate between genuine influence and leadership and just vague activity.

If nothing a teacher does is alien to his job, a prime requisite of a teacher is integrity of character. While integrity of character is not always easy to judge, it is easier to judge than to analyze how the judgment is made. The importance of judging character must not blind us to the equally important tolerance and human understanding in making that judgment. In many moral questions there is a wide range open to honest opinion differences. In making decisions about hiring a teacher, retaining him or promoting him, I do not see how one can avoid taking matters of character into account. Presumably one of the purposes of a university is to develop character in the student. Very likely the indirect influence deriving from the integrity of the staff serves this end better than direct formalized instruction.

Who should evaluate the work of the teacher? First of all we should be interested enough in our jobs as teachers to want to evaluate ourselves. I doubt if there are many of us who do not desire to be good teachers and to improve whatever status of the art to which we have arrived. The fact that you are here is testimony to your interest in improving yourself. But to what extent can a teacher evaluate himself?

Obviously there are many attributes of teaching that can be evaluated by others than by one's self, but certain elements do lend themselves to self-analysis. The teacher probably knows more about his attitude toward his students and towards his subject than anyone else does. He knows something of whether he has his students "with him" in a lecture or a discussion. Student performance on examination and in the laboratory gives him some measure of teacher performance as well.

Certain aspects of the teacher can best be learned from students and, in fact, many teachers encourage regular and systematic student criticism. Students know whether a teacher has a real ability to explain satisfactorily, for to the student this is one of the most important aspects of the teaching process. This is sometimes a difficult feat to accomplish in a class of mixed abilities and with a complex subject. Someone has said that if in instructing a child, you are vexed with it for want of adroitness, try, if you have never tried it before, to write with your left hand, and then remember that a child is all left hand! Students recognize the sympathetic understanding of the teacher who apparently never stops trying to get across his point.

In my first year as a teacher it was my good fortune to teach general chemistry to freshmen. I tried and tried to get across to one student what seemed to me to be an obvious point - that a given weight of copper heated with sulfur would be increased in weight through the formation of copper sulfide. After the third explanation, by a little different approach, I concluded by saying - "isn't that so?" only to get the reply "Well, maybe so, some darn peculiar things happen in chemistry!" I was in despair. The next day the student stopped me in the hall and stated that he had thought about my last explanation for some time and at last "saw the point". I still remember the thrill that the student had in understanding and that thrill I felt, too, when he told me how grateful he was that I had stuck to him in his seeming blindness.

Students know better than we whether we have encouraged them to think. How much actual thinking is going on in the minds of the student is difficult for us to ascertain, but the student knows.

I doubt if any of us believe we are intolerant to disagreement, but many of us are. Here again, I believe the student is a better judge.

Idiosyncrasies which are detriments to good teaching are easily evaluated by the student also. When I was in high school an economics teacher mentioned, usually oftener than once a period, something about what happened "when I was in West Virginia". The result was that we students divided the period into 5 minute units and held a pool each day the winning student being the student who held the 5-minute period in which West Virginia was first mentioned. I suspect that the avid attention of the gamblers was mistaken for rapt attention by the instructor.

On the question of scholarly attainments of the teacher, colleagues can provide the best evaluation. Research activity, publications, day to day discussions, recognition of attainments and many other features, as stated before, provide the clue to the scholarship of the teacher, the depth and breadth of his knowledge and his ability to organize it in a fresh fashion.

This brings us to the last and most controversial evaluator, the administrator. In secondary education the intervention by the administrator is accepted, commonly. Such is not the case in higher education, except when the evaluation is done in an indirect fashion.

In order to continue worthily to perform its fundamental task of teaching, research, and public service the faculty must through recruitment, selection, promotion, encouragement, and cooperation maintain and enhance its strength. There is no more important function of the administration than maintaining and enhancing the quality of the faculty. Success depends on adequate financial and physical resources, on the one hand and sound procedures, accompanied by sound judgment of people on the other.

While a person is on the junior staff, the decision must be made as to whether or not the university wishes to retain his services. Moreover, although this decision may be reached early, competition from other universities, or from non-academic employment, frequently forces new decisions upon the administrator. Secondly, annual decisions as to promotion or salary increases must be made. These should be made on a just assessment of a staff member's value to the university. Thirdly, since it is not possible for all members of the faculty to perform the same duties, it is necessary to determine in an individual case his most effective utilization on research, advanced or elementary teaching and public services. This demands a knowledge of the qualities of a man as well as the needs to be met. Moreover, it is of great importance to both the institution and the individual that fundamental judgments as to man's probable value to the university should be made early. Good practice recognizes the tenure of professors, associate professors, and others who have served a reasonable probationary period. This provides for the security that produces the best conditions for scholarship, the academic freedom necessary to the highest expression of that scholarship, and a check to arbitrary administration.

Although we have talked about many qualities of a good teacher, they can be telescoped into two prime qualities - integrity of character and soundness of scholarship. In my judgment the best way of assuring a faculty having these qualities in abundance is that the administration of the university be in the hands of scholars of high integrity devoted to the maintenance of high scholarly standards.

I believe this paper has demonstrated to you what you already know - that it is easier to recognize good teachers than it is to analyze how such a judgment has been made. Apparently Oliver Wendell Holmes, the physician, was such a good teacher for in Scribner's Magazine for January 1895 is to be found this statment of Thomas Dwight, a student "I lack power to express the weariness, the disgust, and sometimes the exasperation, with which, after 4 or 5 hours of lectures, bad air, and rapid note-taking had brought their crop of headaches and bad temper, we resigned ourselves to another hour. No one but Dr. Holmes could have been endured under the circumstances".

To those of us striving to improve our teaching, a quotation from Aldous Huxley is of comfort. "Good art is everywhere a rarity, and good artists are overwhelmingly outnumbered by bad ones. Among other things, education is an art, and in the field of teaching, as in those of painting, composing and writing, mediocrity is the rule, talent and irresistible vocation the exceptions. In all my years in school and in college I made contact with fewer good teachers than can be counted on the fingers of one hand - two first-rate classical masters, one excellent teacher of biology, and one truly exemplary teacher of English Literature. Four fine practitioners of the art of education out of the forty or fifty by whom, at one time or another, I was guided, instructed, and lectured at. This figure corresponds pretty closely to the world average - one reasonably good teacher in every ten or twelve, one educational genius in every ten or twenty thousand.

"The surprising thing is not that the results of universal education should be so profoundly disappointing. No, the really surprising thing is that they are not much worse than they are. In actual fact the products of education by uninspired teachers are not nearly so bad as the canvasses turned out by uninspired painters. The reason for this is simple and obvious. Canvas is mere dead matter, and can do nothing to make up for the ineptitude of those who daub it. Boys and girls, on the other hand, if they have the wit and the will, turn to good account even the worst educational artistry by the dreariest pedagogue. A canvas cannot paint itself; but an intelligent and lively child can and does educate himself - in spite of bad teachers."

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DISCUSSION

Dr. White expressed some misgivings about the communication between college deans and faculties in the matter of teacher evaluation. Evaluation should involve not only salary increase and promotion, but also improvement in teaching competence. He wondered if Dr. Green had observed any evidence of interest on the part of administrators in providing the type of evaluation that would benefit the student.

Dr. Green replied that "a number of deans do very conscientiously attempt to evaluate their staff members and to (communicate) their evaluation to the staff member in private .... There are others who do .... make such an evaluation for purposes of rank, increases in salary, without discussion." Generalization is difficult because of variabilities in size of staff. Sometimes communication through a department head is necessary. The critical decision in evaluating a teacher involves tenure. When tenure is granted on the basis of expediency, mediocrity is perpetuated, and the staff and students suffer.

Dr. Hargreaves wondered if physicians are trained through medical education to benefit from the consulting services pharmacists are in position to render.

Dr. Green was doubtful that the medical profession is encouraging a receptive attitude. Such an attitude can result from the activities of pharmacists in teaching hospitals and the lectures given by pharmacy personnel to medical audiences.

Dr. Cwalina suggested that authors of the Seminar's papers dealing with syllabi of various courses furnish copies of recent examinations as aids in student evaluation.

Dr. Green suggested that a personal request to the authors probably would elicite the desired response.

In reply to a question of student self-evaluation and student-teacher evaluation, Dr. Green pointed out that the student's appraisal of the teacher could not be correlated with the grades given by the teacher.

In the Texas program for teaching evaluation, a correlation between grades and the students' appraisal of the teacher was reported. Properly applied, these evaluations over the years have the effect of improving the teacher.

Dr. Green strongly urged that student evaluation be restricted to the student and the teacher and that it not be employed for administrative purposes.

In the ensuing discussion, there appeared to be general agreement that student evaluation of teachers should be done exclusively for the benefit of the latter as they objectively strive for greater competence.

Dr. Schwartz commented on the greater reliability of evaluation not only of teachers, but of the whole teaching program, by the more mature graduates who have been out of school for a year or two .

Dr. Smissman suggested that student evaluation of textbooks by the scale with which he was familiar, is quite reliable and beneficial.

Dr. Wilson emphasized the importance that students' identities must be completely anonymous, if their evaluations are to be reliable.

Dr. Webster: "Dr. Green, you can tell by the response you received that your paper has struck a responsive chord, if not a sore spot, and we appreciate the thoughtfulness with which you prepared it. I am sure that the seminarians who receive the printed proceedings of this seminar will take it to heart and probably you will see an upsurge of the most remarkable good teaching in pharmaceutical chemistry in the next two years that has ever been known in the history of Pharmacy."

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Friday Session

Paul J. Jannke

Chairman

THE PHARMACEUTICAL CHEMIST'S HERITAGE AND CHALLENGE IN RESEARCH AND OTHER SCHOLARLY PURSUITS

Walter H. Hartung

The title of this paper was assigned, and for it the Program Committee must accept responsibility. However, what I do with it is entirely up to me. Therefore, with the privilege that is mine I shall first speak about that which is not mentioned in the title but is implied by the character of these meetings. We are all primarily educators, and when we speak of our heritage as specialists and the challenges that are ours we cannot isolate or insulate them from our privileges and responsibilities as professors, namely, to perpetuate knowledge and to be productive scholars. Therefore, even at the risk of seeming trite, let me dwell a few moments on this point.

We are not separate from or an addition to the academic community. Rather we are essential members and an integral component of the community of colleges and universities, in which dislocation or dysfunction in any part affects unfavorably the entire community; and where health and vigor and growth of any part reacts favorably on the whole. A runner, for whom the feet are the sine qua non, may nevertheless be handicapped by a bandaged hand. As members of an academic fraternity and with enthusiasm for our chosen field we are not unmindful of the fact that there may be some of the humdrum and possibly even of vocational guidance or training about our tasks, but there is none-the-less the obligation to let our students know that living is more than the mere earning of a livelihood. We along with our other academic brethren and in harmony with the churches must show that fulness of life is more than getting one's fill with bread or steaks.

Thus we have our most important heritage in the academic traditions and practices that have developed over the centuries and have been entrusted also to us. Our first challenge, then, is to resist the temptations to become parochial. While leading on the young mind we must demonstrate not only to our students but to our colleagues of the faculty as well how, by being loyal to our choice and love of intellectual and scientific endeavors, we are thereby showing our greatest fidelity to our call as teachers.

It follows that we must be loyal to the truth. This could be the basis for a lengthy philosophical and moral discourse, but I shall remind you of only two instances which, had truth not prevailed, might have had uncounted unfortunate consequences. Louis Pasteur, you will recall, first became known as an upstart for daring to point out that his experimental results contradicted the then reigning ideas about spontaneous generation of life; his results were to point the way to the conquest of infectious diseases. In recent years, you will remember, the scientists of the National Bureau of Standards received official rebuke for condemning a proposed additive to storage batteries and not taking into account the "play of the market place." We cannot yield to expediency or profits.

As a corollary we must keep in constant view the fact that basic truths cannot be limited. C. F. Kettering, Sat. Eve. Post, May 17, 1958, p. 45, says:

> "I would advise young inventors and researchers to free themselves of categories, because basic truths have so much more in common than specialists would have you believe."

Perhaps the thought may be expressed in another way, namely, "Beware of modifiers, lest they receive greater emphasis than the noun modified." Several examples will suffice to show what I mean.

The term arithmetic would seem to be quite adequate to describe the science of numbers or the art of computation, and one would hardly presume that its meaning is enhanced or clarified by modifying adjectives. Yet we find in our curricula an offering frequently referred to as pharmaceutical arithmetic. What mystic is this? Are the multiplications different, perhaps? What change to computation occurs when used by pharmacists? Perhaps people who sell buttons ought to be coached in button arithmetic, and dealers in elephants taught in elephant arithmetic. A more descriptive designation might be arithmetic for pharmacists in order to show that this subject is designed to have the student become more proficient in calculations he may be called on to make, and only incidentally intended to correct a deficiency which may have plagued the student since his elementary school days.

We might well examine carefully the titles and also the subject matter of our college offerings. Medical bacteriology and dairy bacteriology? Do their vocabularies differ? Medical biochemistry and agricultural biochemistry? Do they have different versions, say, of the Krebs cycle? Medical pharmacology and Ph.D. pharmacology? Are they different even when the respective candidates are in the same class and work together in the same laboratory and at the same times? And pharmaceutical botany, or do we mean botany for pharmacy students?

Now we come to the matter of pharmaceutical chemistry. I realize that in a group such as we have attending this conference this can be a sensitive question. Yet in fairness to ourselves, to our responsibility as teachers in a professional and not a trade school, to a profession that is alert and alive to its obligations and looking for guidance from faculties, to our students, and to our own academic communities, we should not face away merely because this is a touchy subject. Let me try to state the problem, parable fashion, reviewing the history of the St. Miche family.

THE ST. MICHE FAMILY

The St. Miche family traces its history back to unrecorded times. References to the family appear in the Bible and there is much about it in Arabian lore and history. Eminence came to the famous line when Lanicidem St. Miche appeared on the scenes of history early in the 19th century. The hectic Napoleonic era had closed and the world was preparing for one of its most exhilarating periods of growth. The mind was unshackling itself from taboos and superstitions, and nothing was too sacred for it to question and examine. An unrest quickened the spirit of peoples, a new venture in government, coming out of the New World, was reaching maturity, and the industrial era was to begin, bringing with it a social revolution. This was a glorious time for

Lanicidem. The world was his laboratory, and he was stimulated by everything that came to his attention. An effervescent curiosity caused him fairly to bounce through life.

Primarily, however, Lanicidem was interested in the healing arts, particularly in the role that drugs might play in the curing of diseases and promoting well-being. As an enterprising apothecary he was acquainted with the sources and origins of drugs, and he knew of their virtues and uses. He believed firmly with Paracelsus that the chief aim of chemistry must not be to prepare gold but to make medicine. He also paraphrased another dictum of Paracelsus to say that he, as a professional man, indispensible in the health team, must become familiar with the reactions of elements and compounds in contact with living tissue; he would study these so that he might speak of them as authoritatively as he was able to explain the formation of bubbles when soda was treated with vinegar or muriatic acid, or of the formation of soap when animal fats were allowed to react with potash. His zeal was limited only by the shortcomings of his knowledge, and he was destined to widen the horizons of his generation.

Already Sertürner, a fellow apothecary from Einbeck, had treated opium with fixed alkali and isolated a substance which seemed to be the concentrated essence of the crude drug; it was called morphine. But like other scientific men of his generation, Lanicidem was somewhat slow in comprehending the importance of this fact, the isolation of an alkaline substance from botanical sources; but once its significance was understood, this was to inspire many other similar experiments and the isolation and purification of many such organic bases, subsequently to be known as alkaloids. Also, it now became possible to administer purified agents and thus frequently to avoid in the patient the unwanted side effects, which could now be attributed to undesirable materials in the crude drug.

In 1828 he was one of the many to be stirred by the news that Friedrich Wöhler, a young man in Berlin, had obtained urea without the intervention of the so-called vital force, which had heretofore always been held essential for the preparation of organic compounds. Lanicidem understood at once the significance of this fundamental observation, and he was in the forefront encouraging the growth of a whole new science of carbon chemistry, and for him the climax came when Ladenburg some forty years later synthesized coniine. What was now to prevent the alteration of compounds from natural sources and, perhaps, make available more favorable drugs?

Berzelius from Upsala, professor of botany and pharmacy, though trained in medicine, was providing chemical analyses of some 2000 compounds, many having immediate interest to the energetic apothecary. Also Berzelius was discovering new elements, some of which might be useful in his shop. However, there seemed to be some confusion about the terms element and compound; they were being used interchangeably. Therefore, St. Miche was happy to hear the young Stanislao Cannizzaro once and for all make the distinction clear. Lanicidem was among his first most ardent and vociferous supporters.

At scientific congresses and in personal correspondence he kept in close touch with the young fire-ball from Giessen, Justus Liebig. He actively supported Liebig in launching the ANNALEN DER PHARMAZIE in 1832, and later he and his colleagues

were to be among the notable contributors to this distinguished periodical, which today still thrives as ANNALEN DER CHEMIE.

From Paris came word from Claude Bernard, who started as a pharmacist's apprentice and was to become one of the world's foremost physiologists. Naturally St. Miche and his friends could not risk missing the contributions of Bernard and his students as an understanding of the mechanism of drug action.

The experiments of young Louis Pasteur were followed with the keenest interest and understanding. This young fellow from the French provinces had the audacity to argue with the savants of the French Academy that fermentation is a biological process, that infectious diseases are transmitted by causative living organisms, that immunity is real, and that tartaric acid exhibits a new kind of isomerism. In 1874 Lanicidem was getting to be an elder scientist, but he counted himself very fortunate to read not only in his journals but in the daily press as well that Joseph Lister, a young English physician and independent thinker, was, by using Pasteur's discoveries as a foundation, pointing the way to the conquest of infection in the hospitals. This was particularly gratifying to one who had always believed that they were fools who had prevented Semmelweiss in Budapest from continuing with his empirically discovered aseptic technics and had thus sentenced to die many who had every right to expect life.

There were, naturally, relatives who also bore the family name of St. Miche, and they were no less distinguished. However, we shall follow the descendents of the celebrated Lanicidem because of his special interest for us. Although the records may be somewhat confused, it is well authenticated that he "begat" virile and capable children. The mixup stems from the fact that there was intermarriage with collateral branches of the St. Miche family, and the inheritance through Lanicidem is difficult to separate. It is certain, however, that he is the father or the father-in-law of the following, Cinorgain, Cinorga, Alanytic and Alpha Carmeutic, the last almost certainly being the oldest son of Lanicidem. These have all been very prolific, perpetuating ancestral names and adding new ones, among whom should be mentioned especially Caliphys, Coidoll, and Colligobia. As might be expected, all branches are giving a good account of themselves.

Members of the St. Miche family have migrated to all parts of the world, and it is with those who have come to the United States that we are more especially concerned here, where they entered with vigor and commendable zeal into the total cultural, social and economic life and structure of the country. Although their presence and citizenship was little recognised until the advent of the First World War, none would now say that they have betrayed their heritage or been unfaithful to the family tradition. In fact, the founders of the family might well be forgiven if they viewed with disbelief the achievements of their offspring. Nevertheless, the St. Miche family history in the United States shows one peculiarity which it may profit us to contemplate.

The children of Alpha Carmeutic, whom we shall call Alpha for brevity, agreed to be primarily responsible for the science and art of the apothecary after the tradition of their patriarch Lanicidem. They were proud of their patrimony and naturally jealous of their prerogatives. Unfortunately, whatever the reason, they deviated in vigor, enthusiasm and broad interests from Alpha's father. Perhaps the odds of a new country and expanding frontier were overpowering. Or perhaps the siren call of commercialism became irresistible. In any event, one might suspect that the "front" developed by the

apothecary shop assumed proportions somewhat like the caudal appendage which wagged the proverbial dog. Medicine and pharmacy, some fifty years ago, manifested some common disquieting symptoms. Medicine, by assuming stricter control over its ethics, education and the practice of its devotees, literally lifted itself by its own bootstraps to new and enviable heights. The sons of Alpha chose to procrastinate; when much later they took similar action, they did so with too little and too late. Not even by the temporary expedient of conferring on themselves the title of pharmaceutical chemist could they close the gap. This is, of course, regrettable and unfortunate.

But even more unfortunate, it would seem, is the fact that of Lanicidem's descendents that branch coming through Alpha Carmeutic has become somewhat alienated from the other members of the St. Miche family. It appears as if they have deliberately limited their horizons, and one is tempted to ask whether they have conferred unprecedented dimensions on adjectives.

Let it not be said, however, that the children of Lanicidem have betrayed this ancestor. In the field of drugs alone they have worked miracles; therapeutic agents are constantly being discovered and their potency and efficacy are being enhanced. Nevertheless it is pertinent to inquire whether the sons of Alpha have not resigned at least some of their heritage to relatives from whom, as mentioned above, they seem to have alienated themselves. For example, of the new drugs introduced since 1900, how many did they provide when, one might expect, they should have provided a major proportion? Or again, of the new drugs, how many structures were solved by them? Even in pharmaceutical formulations have they given their quid pro quo to Caliphys and to Coidoll? And of what help have they been to Colligobia? It is true enough that all the members of the St. Miche family have a fraternal obligation to Alpha's children; is there not also a reciprocal obligation? Especially in matters pertaining to drugs?

The substance of this family history is correct. Interpretation may vary with individuals reading it. The heritage of the pharmaceutical chemist speaks for itself. Can we ignore the challenge?

The title of this paper includes the phrase "and in other scholarly pursuits." This has already been discussed in part in connection with our privileges and duties as responsible members of the academic community. I ask you to bear with me while I bring up another point. Perhaps I can do this better by reminding you that a man trained in one area frequently becomes invaluable in a field appreciably different from his training. We all know of engineers who have become excellent executives or administrators, or personnel managers. Not infrequently a law graduate becomes a better merchant or accountant than the graduate of a school of business administration. A politician may become an educator, or vice versa. We are fortunate to have a pharmacy-pharmacology trained scholar and researcher as president of the Medical College of Virginia. (One is tempted to suggest that the hucksters of Madison Avenue might with considerable advantage try recruiting at seminaries.) It is precisely the training of these men, coupled with their personality, which makes them valuable where they are.

Such being the case, I am not disappointed when someone who has presumably trained himself for a career in pharmaceutical chemistry elects to work in another field. Rather I take satisfaction in seeing that we have not trained him so narrowly as to make his efforts elsewhere less effective or unprofitable. He leaves as a friend and a living example of our best efforts.

In line with these thoughts I feel we owe a vote of thanks to the administrators of the American Foundation for Pharmaceutical Education for their liberal and understanding policy in awarding grants.

THE PHARMACEUTICAL CHEMIST'S NEED AND OPPORTUNITY FOR POSTDOCTORAL PROFESSIONAL DEVELOPMENT

J. H. Burckhalter

Despite the fact that I have supervised the programs of postdoctoral students and recently held a Fulbright appointment, I do not presume to speak authoritatively on the subject of this paper because there are such highly varying needs and opportunities for study at the postdoctoral level. Nevertheless, based upon my experience and reading, I shall try to acquaint you with my thoughts on the subject.

The title of the topic which I was assigned contains the word need in reference to postdoctoral study. If need be used in place of its synonym necessity, then perhaps it is too strong a word, for I doubt if many of us would describe special study beyond the doctor's degree as an absolute necessity. Nevertheless, in Germany, intense study and research beyond the doctorate is a requisite for those who wish to attain the rank of professor. Even in America, particularly in certain scientific areas where there are more aspirants than desirable teaching posts, experience as a postdoctoral student has become a virtual necessity. This is particularly true in organic chemistry where frequently the successful candidate for an excellent teaching position has held more than one postdoctoral appointment, one of which might have been abroad. It should be said parenthetically that such a practice probably has a very favorable influence upon the quality of teaching and research.

Before enlarging upon the advantages of postdoctoral study, for the sake of objectivity we should briefly consider circumstances under which it might be undesirable or difficult. A professor or an industrial researcher with a very active research program might find it difficult to leave his students or workers. For example, I knew an eminent scientist who was reluctant to attend scientific sessions, because any time spent away from his laboratory was truly a misuse of time so great were his ability and contributions to science. I believe that it can be said without hesitancy that the scientist in question would have lost far more than he would have gained by spending a year in another institution. Also, there are considerations of a personal nature which would prohibit one from spending a year as a postdoctoral student or visiting professor, and all influencing factors should be carefully weighed before a decision is reached to apply for a year's leave. Undoubtedly, a large number of pharmaceutical chemists who would profit from such an experience have been deterred by the difficulties which can be easily visualized.

There would appear to be two opportune periods in one's career for postdoctoral study. One comes immediately following the attainment of the doctor's degree and the other comes after some years of industrial work, teaching or other type of institutional experience. The recent Ph.D. recipient is in an admirable position to broaden his background by moving to another institution where he can become exposed to a different type of research or an area of research of special interest and where he can widen his professional acquaintanceship. Most scientists agree that one should attend more than a

single institution during his academic career. It would be difficult to evaluate fully the rewards resulting from increased professional contacts. Also, as we have already said, there appears to be a definite trend toward postdoctoral training by the young scientist who wishes to enter teaching.

A number of professors of pharmaceutical chemistry have received postdoctoral students in their laboratories. Having supervised the progress of ten - five from this country and five from abroad, I venture to insert, during this part of the discussion, certain conclusions which have been drawn from my experience and from that of some of my colleagues. One professor summarized his sentiments by saying that certain postdoctors are a hundred times better than others. I fully confirm this view. Then, postdoctors from Europe may often be excellent laboratory workers and they may know the limited field of their doctoral research very well, but there may be gaps in their general knowledge of the broad field. Many postdoctors, having recently attained the goal of the Ph. D. degree, lose their enthusiasm for research, and thus produce much less than graduate students. Besides desirable personal qualities and native ability, I look for the following characteristic in a postdoctoral candidate: love for the laboratory, library and seminar.

A researcher or teacher who has remained in the same environment for a number of years may have reached a state of intellectual and physical stagnation. A change of scenery or activity for a year may prove to be a great asset to him, as well as to his students or fellow workers. Unlike the great scientist previously mentioned who felt the need to remain always in his laboratory, another very productive research professor I know has a temperament which requires him to spend one year out of four away from the environment of his University. It is likely that even the most inspiring lecturer and productive researcher loses effectiveness after several years of the same regimen. This need for a change in activity or scenery by professors was recognized when the sabbatical leave was instituted.

I shall briefly mention the cases of a few pharmaceutical chemists who felt the need to study or work for a year in a different environment. One was an industrial researcher who wished to gain experience in the separation of natural products by such means as the technique of counter-current distribution. One professor, who took his degree before electrons were widely used, wished to study as a means of adapting the electronic theory to the teaching of the chemistry of organic medicinal agents. Another professor who had not done research since his doctorate wished to get back into the habit of working on his feet by taking a postdoctoral research grant. Still another professor who is both an excellent research director and classroom lecturer, nevertheless, felt strongly the need to approach perfection in teaching by spending a year in observing the methods of a number of professors in a large university. Another professor in a field closely related to ours felt impelled to teach a course for a year in a university which had no offerings in pharmaceutical or medicinal chemistry, and the U.S. Public Health Service made it possible. Another acquaintance who is a research chemist in a large institute spent a year as a researcher in a German University because he wished to gain an insight into the wisdom of a German chemist who is known for his fundamental and original ideas. I myself was led to spend a year in a German institute of pharmaceutical chemistry because I wished to gain greater insight, primarily historical in nature, into my chosen field. I might add that my membership on a local Fulbright Committee and a Foreign Students' Scholar-

ship Committee helped to keep before my eyes the objectives of and the opportunities for posdoctoral study, particularly in a foreign country.

The awarding of grants for postdoctoral research and teaching appears to follow the rule of Markonikoff: that is, those who have less need than others for such experience most often are those who seek and receive it. In general, one who has excellent transcripts, numerous publications, splendid letters of recommendation and a well-planned proposal becomes a strong candidate. But it is my opinion that slight weakness in the first two requirements can be largely offset by strength in the last two. So, it would behoove one to pick recommenders who understand him well and who are likely, therefore, to write favorably of the applicant. Do not make the mistake of asking a letter of the type who has never been known to write an enthusiastic letter about anybody.

In connection with the proposed objectives of an application, a sincere statement of well organized and worthy aims carries much weight. Further, a copy of a letter of invitation from the host institution enclosed with the application is often an effective instrument.

One of the first questions to arise in connection with a postdoctoral grant concerns finances. In general, the young applicant who has recently received the doctorate and who is accustomed to a modest or inadequate income experiences no difficulty in accepting the stipend offered him. However, it is frequently a different matter for the older, established professor or industrial scientist. Perhaps the most favorable arrangem ent is one which allows the applicant to receive a sabbatical grant from his university in addition to a Fulbright or other award. Also, Guggenheim awards may be received along with another grant. In the early days of the Fulbright awards, it is understood that one could support a family in excellent fashion without supplementary funds. Now one's family cannot live in the fashion to which it has been accustomed solely on the basis of the award, and in order to travel extensively and eat and live as at home, a matching sum would be needed. However, in general if one would travel little and live according to the standards of those around him, whether he be in the United States or abroad, the stipend customarily awarded by most sponsors will prove to be adequate. Further, the amount of many awards is based upon the size of the family of the grantee.

What opportunities for postdoctoral study or teaching are available to pharmaceutical chemists? While I shall outline in brief form many of those which are presently available, the interested person might also consult a large library and the offices of the graduate and pharmacy school in a university.

Particularly appropriate for teachers in the pharmaceutical sciences are the Gustavus A. Pfeiffer Memorial Research Fellowships. The awards are made through the American Foundation for Pharmaceutical Education. They are "designed to encourage pharmacy faculty members to engage in sound, original investigations either as full time research projects, or as substantial though part-time projects, in conjunction with a teaching assignment." These fellowships provide a stipend adjusted to the previous income level of each fellow. An allowance for supplies and technical help may also be granted.

Candidates interested in postdoctoral research or university lecturing abroad under the Fulbright Act should write to the Conference Board of Associated Research Councils, 2101 Constitution Avenue, N.W., Washington 25, D.C. In countries where the Fulbright Act is not in operation, in other words where the United States does not have assets left

from World War II, lectureships may be held under the auspices of the Smith-Mundt Act. These are usually arranged for when a foreign university makes a special request.

Two well known organizations use their names jointly as the National Academy of Sciences - National Research Council, at the same address given in the foregoing paragraph. This organization invites applications for postdoctoral fellowships by those of promise and ability who generally have not reached thirty-five years of age. This organization screens applicants for grants made by the following sponsors:

American Cancer Society
Lilly Research Laboratories
Merck and Company (Senior Postdoctoral grant)
James Picker Foundation (Radiological research)
National Research Council (Postdoctoral fellowship in medical sciences)
British American Exchange (Postdoctoral fellowship in cancer research)
National Science Foundation (Senior Postdoctoral fellowships and Science Faculty fellowships)
Argonne National Laboratory and Oak Ridge National Laboratory (Postdoctoral Resident Research Associateships for basic research in the biological and physical sciences. Annual gross stipend $7,035.)

Particular attention is called to the Science Faculty Fellowship Program of the National Science Foundation which was mentioned in the foregoing list. Under this program, awards are made to college teachers who wish to pursue an individualized program of activity designed to enhance their effectiveness as teachers of science, mathematics or engineering. Eligibility requirements include a baccalaureate degree and three years of college teaching experience.

Other grants for which pharmaceutical chemists appear eligible are briefly listed as follows:

U. S. Public Health Service (Postdoctoral research fellowships. Training abroad allowed only if not obtainable in the United States. Apply to Research Fellowships Branch, Division of Research Grants, Bethesda, Maryland).

John Simon Guggenheim Memorial Foundation, New York 17, New York (30 to 40 years of age; ability for creative research.)

Damon Runyon Memorial Fund for Cancer Research, New York 17, N. Y. (Under 40 years of age.)

Eisenhower Exchange Fellowships, Inc., New York 21, N. Y. (Ages 25 to 40.)

Life Insurance Medical Research Fund, New York 17, N. Y. (Research on cardiovascular problems.)

American Association of University Women, 1634 EYE Street, N.W., Washington 6, D. C. (Excellent grants for women.)

Lalor Foundation, 4400 Lancaster Pike, Wilmington 5, Delaware. (Research grants in chemistry, physics and the biological sciences.)

American Scandanavian Foundation, 127 East 73rd St., New York, N. Y. (Independent research in the Scandanavian countries.)

Belgian American Educational Foundation, Inc., 420 Lexington Ave., New York 17, N. Y. (Research in Belgium or Belgian Congo.)

American Swiss Foundation for Scientific Exchange, Institute of International Education, 1 East 67th St., New York 21, N. Y. (Advanced study or research in natural science and medicine. Doctor's degree or equivalent in experience.)

Weizmann Institute of Science, Rehovoth, Israel.

The professor who wishes to bring postdoctoral researchers into his laboratory, of course, may encourage the candidate to apply to some of the sponsors which have been mentioned. Also, as a principal investigator, the professor may apply for a research grant through governmental, industrial or foundation sources, which will enable either an American or foreign scientist to join him as a research associate.

Besides the opportunities which are available through well known sponsors, other possibilities should not be lost sight of. Perhaps you and a colleague in another institution in this country or abroad might arrange to exchange positions, homes and even salaries for a year. Or perchance you hear of a pharmaceutical chemist who wants to spend a sabbatical leave abroad; you might fill his post for a year. Of course, such possibilities as these are made more likely by contacts at meetings and by direct inquiry concerning such possibilities. In making inquiry, you will no doubt write to the Conference Board of Associated Research Councils in Washington where a registry is kept of persons who are interested in various sorts of research and teaching experience at other locations. Further still, UNESCO, 16 Kleber Ave., Paris France, publishes a booklet entitled, "Teaching Abroad" which lists both places and persons who are available.

In making arrangements for an exchange of positions or for any other program which does not provide travel to or from a foreign country, application should be made for a Fulbright travel grant by professors or industrial researchers in either country.

A final but important word should be said in connection with an application for a postdoctoral grant. Because of the misunderstanding created in the minds of reviewers by use of the title of pharmacist, the pharmaceutical chemist should apply under the latter title. There is no doubt that the title of pharmacist creates an image of a dispenser of drugs and miscellaneous items in the minds of certain reviewers. They next wonder if such an individual has a place in a postdoctoral or exchange program.

DISCUSSION

Dr. Jannke wondered if Dr. Burckhalter didn't agree with his observation that because of the economical situation in this country most new Ph.D.'s found it to their family's advantage to foresake post-doctorate work and enter into teaching or industry so as not to waste time achieving their full earning capacity. Such a move drains away from our institutions the potentially rich reserve of post-doctoral fellows who perhaps are at the peak of their enthusiasm if not at the peak of their intellectual capacities.

Dr. Burckhalter agreed emphatically and repeated a point he made earlier that the ideal time for such study was immediately following the granting of the Ph.D. degree. The person is not yet used to receiving a handsome income and following his study period he will not be shocked when he accepts an even more handsome job opportunity.

Dr. Jannke concluded that post-doctoral fellowships were like a two-way street when it came to benefits derived. Along with the monetary rewards there were the personal satisfactions from continued education as well as accomplishments in a given field of study.

Dr. Small wondered if it be a just claim that post-doctoral study was necessary because the Ph.D. programs were inadequate. It seemed that the engaging of a fresh Ph.D. for post-doctoral work was motivated for selfish reasons. He agreed with Dr. Burckhalter that post-doctoral work was much more desirable after a person had gained several years experience and could thus enrich and refresh himself with this new training.

Dr. Osol thought that Dr. Burckhalter's suggestion of exchange - professorships was excellent but wondered if the program would work out beneficially to both parties since the German scientist received a much greater salary than his American counterpart.

Dr. Burckhalter thought perhaps that the exchange rate had not been applied to the figures that Dr. Osol quoted. In real figures he felt it would be rare for them to earn an equivalent of $6000 American money.

Dr. Higuchi wondered if the period of acclimatization was the same for the American professor abroad as for the European professor in America.

Dr. Burckhalter agreed, using his case as an example. He thought it was rare when an American in Europe could accomplish a tremendous job in research.

Dr. Higuchi wondered if this didn't adversely affect our position overseas.

Dr. Burckhalter - The people who hurt us more overseas are sport-shirted, loud-spoken people. These are not generally University people. The high regard of these peoples for a professor is carried over to the visiting American professor.

CONTRIBUTIONS TO RECORDED KNOWLEDGE BY PHARMACEUTICAL CHEMISTS

Justin L. Powers

The title appearing on the program may be misleading unless the subjects I was requested to discuss are explained. These include (1) what the pharmaceutical chemist should write, (2) where he should publish, (3) planning a text, (4) preparation of manuscript, and (5) responsibility of referees, editors, and Editorial Advisory Board members in maintaining standards of a journal and their relationships with authors. Perhaps "Off the Editor's Chest" would have been a better title than the one assigned.

Papers published by pharmaceutical chemists are probably called contributions because the authors are not paid at line rates or by the word. Their rewards for publishing papers are less tangible, but nonetheless real. If papers have substance and are well-written, they add to the morale of the authors by giving them a feeling of accomplishment, increase their prestige, and often contribute to winning promotions, prizes and awards. Of even greater importance, scientific contributions of high quality also enhance the reputation of a profession by enriching its literature.

What the pharmaceutical chemist writes should be of significance, but it is impossible for anyone to advise him on this point except in a very general way. The function of the Scientific Edition of the Journal of the American Pharmaceutical Association is to publish all contributions which represent original, valid, and significant research of pharmaceutical interest. Perhaps this might be offered as a criterion of what the pharmaceutical chemist should write and publish.

Although the pharmaceutical chemist has several media for publication from which to choose, I would like, of course, to see all pharmaceutical chemistry papers published in the Scientific Edition of our Journal.

Preparation of a Manuscript

One of the most important phases in the publication of scientific articles is the preparation of a manuscript, a step which follows the accumulation of sufficient data to warrant its presentation.

Consistency of Style. -- When language is used in connection with a rapidly developing subject such as chemistry, there can be no unalterable rules for terms, abbreviations, and style of presentation. Nevertheless, an editorial office has to strive for a reasonable degree of consistency and must have certain working rules. Some of these are spelled out in our "Notice to Authors of Papers," which is published from time to time in the Journal. Judging from some of the manuscripts we receive for publication, this notice is ignored altogether too frequently. As a start in the preparation of a manuscript for publication in any scientific journal, the ground rules spelled out in directions to authors, if available, should be read carefully and followed.

Another good habit for an author to form is to scan several articles in a recent issue of the periodical to which his finished manuscript is to be offered for publication, and to note carefully the style, arrangement, and orthography of articles comparable to his. He should then follow as closely as possible in his manuscript the accepted style he has observed. Literary style is much more circumscribed in scientific papers than in nearly any other type of writing, and a contributor to a scientific journal should not feel reluctant about imitating the style and presentation of a well-written paper comparable to the one he intends to write.

Clarity and Brevity. -- Clarity is essential in all scientific writing. One of the most effective ways to attain clarity is by brevity. A simple sentence is easier to understand than a more complex one. Unnecessary adjectives are awkward, and subordinate phrases are likely to be confusing. Often a topic sentence will serve adequately in place of a paragraph covering half a page of manuscript. Conciseness in presentation of data in figures and tables is also essential. As a general rule, data should be given in one or the other, but not in both. A good illustration can often supply information which would require several paragraphs of explanation in the text.

A well-planned outline will aid an author in achieving brevity and attaining clarity. It will enable him to assemble his material logically by numbering and lettering the sections and subsections in proper sequence. By this device, he can also arrange and rearrange parts of the text, tables, figures, and footnotes more easily than in a completed manuscript. No two authors, attempting to write a scientific paper, will use exactly the same approach to the task. It should be remembered that there is no way of writing well and also of writing easily.

Punctuation. -- On questions of punctuation either "The Manual of Style,"[1] or "The Secretary's Handbook."[2] may be used advantageously. The authority to follow on spelling, hyphenation, and comparable points is the latest edition of "Webster's International Dictionary."

Nomenclature. -- Chemical nomenclature should be consistent and conform to the usages of Chemical Abstracts. When in doubt, authors should refer to the indexes of Chemical Abstracts, "The Naming and Indexing of Chemical Compounds,"[3] "The Ring Index,"[4] and reports and pamphlets of the American Chemical Society Committee on Nomenclature, Spelling, and Pronunciation.[5] It is sometimes awkward to conform rigidly to a set of rules throughout a manuscript, and this is not required. If brand names, trivial names, generic names, or code or letter designations are used, the corresponding approved chemical names should also be given at least once, and preferably where the other types of names first appear in the manuscript.

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[1] Published by the University of Chicago Press, Chicago 37, Ill. Often referred to as the "Chicago Manual of Style."

[2] Sarah Augusta Taintor and Kate M. Monroe, "The Secretary's Handbook - A Manual of Correct Usage." The Macmillan Co., New York, N. Y.

[3] Introduction to the 1945 Subject Index of Chemical Abstracts.

[4] A. M. Patterson and L. T. Capell, "The Ring Index," Reinhold Publishing Corporation, New York, N. Y., 1940.

[5] Available from the Office of Chemical Abstracts, The Ohio State University, Columbus 10, Ohio.

Typescript. -- It will be of great assistance to the editor, and to the advantage of the author, if the typescript of a paper is prepared in form and style as nearly identical as possible with those of comparable printed articles appearing in the periodical to which the manuscript is to be offered for publication. The less time required by the editorial office in the mechanical aspects of preparing a manuscript for publication, the more time can be given to correcting and polishing the text. Moreover, manuscripts requiring a minimum of directions to the printer and engraver are often published more promptly than those requiring several hours of effort on the routine mechanical aspects of marking copy for advancement to type.

Titles, By-Lines, and Synopses. -- Let us start with the title. In a well-arranged manuscript the title is centered on the first page in the shortest possible form consistent with clarity. The first letter of each word in a title, except articles, conjunctions, and prepositions, is capitalized. Only words to be italicized are underlined. If more than one line is required, double spacing is used. Deviation from this arrangement places an unnecessary burden on the person who prepares the paper for the printer.

The names of the authors, preceded by the word "By," should be centered four or five line spaces below the title. The source of the manuscript and the identity of the authors should be given in footnotes as illustrated in articles published in the Journal.

An introductory synopsis should also appear on the title page with the margins indented more than in the text. It should be written concisely in normal English with few abbreviations and without documentation. Pronouns, if used, should be in the third person. The first sentence or two should indicate the objectives of the investigation. Newly observed facts and the conclusions drawn from the experimental work discussed in the paper should be outlined briefly. No introductory synopsis should exceed 150 words, and longer ones will be cut. The author should assume that the reader has some knowledge of the subject. The introductory synopsis should make a summary unnecessary.

The Body of the Article

Introduction. -- One or two introductory paragraphs should follow the synopsis, but should not be identified as such by a center heading. The introduction should indicate the intention and meaning of the investigation and the method of procedure. Lengthy documented reviews of the literature should not be included in the introduction or elsewhere in the manuscript.

Section Headings. -- Center headings should be confined to such divisions as "Experimental," "Discussion," and "References." Subheadings usually should be indented and run into the part of the text to which they apply. Sometimes, however, additional subheadings flush with the left-hand margin are necessary. When more than two subheadings follow a main center heading only two will be used, and the editor may choose the wrong ones.

Mathematical Material. -- Authors of papers including data requiring mathematical treatments are responsible for the typographical correctness of equations and they should strive to avoid ambiguities. For example, if equations are typed, it is necessary to distinguish between the letter "l" and the figure one, between zeros and "O's," and between a multiplication sign and the letter "x". Few typewriters are equipped with

Greek letters, and they must be hand written. Handwriting is often difficult to decipher, but errors can be avoided by drawing a line from a Greek letter, or any other unusual character, to the margin and spelling out what is meant instead of leaving it for the editor to interpret as best he can. Subscripts and superscripts must be very carefully positioned in an equation, and indicated by carets and inverted carets respectively. This is particularly important in subscripts to subscripts.

One of the most troublesome features in marking mathematical equations for the printer is deciding whether to use built-up fractions or slant lines. In printing, the oblique stroke, or solidus, should be used wherever possible because built-up fractions break into the line above and below. This presents a clumsy appearance and adds to the production cost. When equations are numbered and referred to in subsequent expressions, it is preferable to center them on the page with the number of the equation flush with the right-hand margin. When built-up fractions are used, space should be left above and below the line separating the numerator from the denominator. This facilitates the work of the editor in identifying the characters and indicating the style of type in which they are to be set. Typographically perfect mathematical data in manuscripts will avoid costly corrections after papers have been set in type. The meanings of terms in equations should be run in, separated by semicolons, and not arranged in a column.

Tables. -- Directions given in our "Notice to Authors of Papers" for the preparation of tables should be followed, but few contributors observe them. Tables are often submitted without titles, without being numbered consecutively with Roman numerals, without being mentioned in the text, and with no thought having been given to typography in writing column headings. Most tables are submitted with lines of type single spaced and each column of data with a "fence" around it. Here again I would like to urge all authors of papers to construct typewritten tables so that they will resemble as closely as possible those which appear in the printed pages of our Journal, except that double spacing should be employed throughout.

Figures. -- Graphs, diagrams, and photographs are every bit as important as the written word for the expression of scientific ideas. All authors of scientific papers realize the importance of illustrations, yet a large majority use very little imagination and exercise only slight care in preparing them. Probably most authors of scientific papers are neither draftsmen nor artists. The best procedure for them to follow is either to have their graphical illustrations prepared by professional draftsmen, or to provide themselves with proper equipment and teach themselves the necessary techniques. A good guide for anyone inexperienced in preparing graphs or diagrams is "Engineering and Scientific Graphs for Publication,"[6] which can be obtained for a nominal sum.

Line drawings, to reproduce satisfactorily, must be made with India ink on white tracing paper or tracing cloth with specially designed lettering pens that can be used for drawing lines of various widths. Drawings should be designed for reduction in width to one column, slightly less than 2-3/4 inches, and only in exceptional instances to two columns. It is most convenient for the editor and the printer if drawings are

[6] Available from The American Society of Mechanical Engineers, 29 West 39th Street, New York, N. Y.

made letter size (8-1/2 x 11 inches) with relatively wide margins, so that the long dimension is 9 inches or less. A clear space of 1 inch or more around all drawings is necessary to permit markings by the editor for the guidance of the printer and engraver.

All lettering must be large enough so that it is legible after reduction. A good rule to follow is that the height of capital letters after reduction should not be less than 1/16 inch. If the reduction is to be 3:1 the original lettering should be at least 3/16 inch high.

A simple style of lettering such as the Gothic, with its uniform line width, should be used. Lettering templates and pens[7] are absolutely essential to insure an even, uniform appearance. Ordinary typewriter lettering is not large enough or black enough to be satisfactory. Authors are urged never to place the title of a figure on the body of the graph. The title should be typewritten and preferably separate from the figure since it will be set in type. Unless captions are very short, the parts of a figure requiring explanations should be lettered or numbered and typed copy corresponding to the identifying marks should be provided to be set in type following the title. Under no circumstances should a caption be written as an extension of a line or curve of a graph. Every figure should be mentioned in the text of the paper and each one should be identified with its appropriate number, the names of the authors, and an abbreviated title of the paper to which it relates, written on the upper or lower edge of the page. If this is not done, it often leads to confusion.

Structural Formulas. -- Many structural formulas in manuscripts submitted for publication are, to put it mildly, rather weird. They are likely to be quite distorted and it is frequently impossible at a glance to determine whether an element is a part of a cyclic compound or the beginning of a substituent group. Printers, as a rule, are not chemists and it becomes necessary for the editor to redraw structural formulas undecipherable to the uninitiated. Satisfactory structural formulas can be drawn easily by using a stencil readily obtainable from nearly any laboratory supply house. In cyclic compounds all double bonds should be indicated and substituent groups should be carefully aligned with bond lines from the parent compound. All lettering should be typewritten with subscript numerals clearly indicated.

Abbreviations for Periodicals. -- The names of all periodicals cited in a list of references must be abbreviated according to the conventions used by Chemical Abstracts in its List of Periodicals Abstracted.[8] It is surprising how seldom contributors to the Scientific Edition of the Journal observe this requirement. Many of them persist in using such abbreviations as A. C., J. B. C., J. A. C. S., J. O. A. C., J. A. Ph. A., I. E. C., and almost unintelligible abbreviations for other periodicals.

Correcting errors in abbreviations for periodicals by the editorial staff should not be necessary, and yet it consumes a considerable amount of time. It seems as if it is

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[7] "Wrico" templates and pens are available from the Wood-Regan Instrument Co., Nutley, N. J. "Leroy" instruments may be obtained from Keuffel and Esser Co., 127 Fulton St., New York, N. Y.

[8] The latest List of Periodicals Abstracted was published in Chemical Abstracts, 50 (1956), as a part of the Author Index. Reprints may be purchased from the American Chemical Society, 1155 Sixteenth St., N. W., Washington 6, D. C.

not asking too much of contributors to follow a convention as simple as the one used for abbreviations of periodicals cited in references.

Editorial Responsibilities

Referees and Editorial Advisory Boards. -- One of the major functions of an editor of a scientific periodical is that of selection of papers to be published. Most editors lack the specialized knowledge to appraise and evaluate the technical and scientific accuracy of all manuscripts submitted for publication. The necessary knowledge must be supplied by referees, reviewers, and members of editorial advisory boards. The editor should use good judgment in selecting referees, but even this does not always insure the selection of only papers of high quality.

We are all interested in bringing about an improvement in the quality of papers finally accepted for publication. A conscientious referee can be of great help in guarding against the acceptance of papers of inferior quality. Unfortunately, some referees either do not have the time or the inclination to devote sufficient effort to the review of papers assigned to them. As a result, occasional papers are recommended for publication which possibly should not have been accepted. Appraisal of the quality of a paper requires a considerable amount of time and effort and unless a referee is willing to devote sufficient attention to papers he is requested to review, it would be well for him to return them to the editor and suggest other referees who might be in a better position to do the job.

A good review states, first of all, whether in the opinion of the referee the paper should be accepted for publication. If it is not recommended for publication, the reasons should be given. If the paper is recommended for publication, a referee can render a very great service to the editor and to the author if he offers suggestions for revision and condensation. The indication by reviewers of deviations from established style and form of presentation also adds greatly to the effectiveness of a review.

Occasionally differences arise between authors and referees which cannot be reconciled and the editor may form the opinion that both are too unyielding in their attitudes. In instances of this kind he may call upon one or more members of the Editorial Advisory Board to assist him in making a decision. Members of the Board are also called upon to serve as referees. They are expected to call upon colleagues who may be better qualified to evaluate parts or all of some manuscripts than they are themselves. This is frequently done by Editorial Advisory Board members connected with universities, pharmaceutical manufacturing establishments, or research institutes. Through their efforts we often obtain a consensus of several people instead of the opinion of only one. Other referees who are not members of the Editorial Advisory Board are urged to follow the same procedure. When an editor requests the services of a referee, he is somewhat hesitant about setting an arbitrary time limit for the completion of a review. A referee should place himself in the position of the author and be guided in the promptness of the preparation of a review by the kind of service he considers reasonable for the review of his own contributions.

Editors. -- One of the important aspects of editing a scientific journal has to do with the mechanics of the job. The editorial office prepares a manuscript so that the typesetter's task will be made as easy as possible. Sizes and styles of type to be used

are indicated, headings and sections are marked, and directions for converting line drawings and photographs into line cuts and halftone cuts must be given. Tables have to be marked so they can be set in legible form and equations often need to be rearranged to conform to a compromise between legibility and reasonable cost. Corrections are often made in grammar, spelling, punctuation, and abbreviations to conform to the established Journal style. The manuscript is then forwarded to the printing plant. Galley proof is read against manuscript copy, and the galley proof is then paged by pasting it on forms. This is followed by page proof which is again carefully read.

It may appear that mechanical editorial skills are easily acquired, but in a journal which publishes papers covering a large number of subjects, it seems as if some new technical problem arises in connection with a large majority of the papers processed. Many of these unexpected problems could be avoided if authors would only exercise greater care in writing, editing, and rewriting their manuscripts before sending them to a periodical for publication. This is a responsibility that authors shirk altogether too frequently and one to which more attention should be given. Greater care in the preparation of manuscripts will insure more prompt publication by making it unnecessary to return papers for revision and to spend an inordinate amount of time preparing them for the printer.

In a recent article entitled "How to Edit a Professional Journal--and Survive," Henry Clepper,[9] the Managing Editor of the Journal of Forestry, summed up the qualities an editor should possess as follows:

> "He believes that the literature of his profession is one of its most precious assets for it is the permanent record of the growth of scientific and technical knowledge. Within his power and limitations he strives to assure that his journal shall fulfill its principal responsibility--not only keep abreast of new knowledge, but to keep in advance of its possible application."

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[9] Am. Inst. Biol. Sci. Bull., 8, 23(1958).

DISCUSSION

Dr. Taub stated he had experience with a project of a literary nature in which a student had to prepare a new drug application which would be acceptable to the Food and Drug Administration or prepare a patent application or a publication based on a thesis previous to a masters or doctorate degree. (These assignments would tend to give the student the needed experience in preparing material for scientific publication.) These reports would then be critically evaluated by the faculty members in the specific area of the report. He wondered if Dr. Powers felt that this program might help the future problem of accurate scientific writings.

Dr. Powers replied that indeed this would and hopefully wished that graduate students had more such type training.

Dr. Gisvold raised the point that today's trends are toward the use of conformational formulae in publications and wanted to know if the journal were ready to accept these structures.

Dr. Powers replied that if the formula is relatively simple it can usually be built up from the type, but if it is very complex and involved then a lined drawing should be prepared and be used for reproduction of the structure.

Dr. Gisvold questioned the referee's right of requesting an author to express his results in such a way that the originality is lost or the style so changed that the author no longer recognizes his own original thoughts.

Dr. Powers agreed with Dr. Gisvold that the referee would have gone beyond his duties but wondered if the editor had ever insisted that he use a recommended style. To which Dr. Gisvold responded, no, but he often wondered whether the editor sided with the referee.

Dr. Higuchi acknowledged the able assistance rendered the authors by Dr. Powers. He asked if Dr. Powers had made any progress toward expanding the Journal as was suggested at the A.A.C.P. meeting in Los Angeles. Powers said that no progress had been made to date since the process involved a special committee being formed by the elected members of the Council and the Committee on Publications and there have been no meetings of either group up to this time.

Dr. Webster wondered whether a section in the Journal could be devoted to notes and communications to the editor much the same as presently found in the Journal of the American Chemical Society. Dr. Powers explained that the Journal provided such space but that few contributors made use of it.

Dr. Discher: Did the editor ever bring in especially qualified reviewers when there were certain differences of opinion between author and referee? Further, how did the editor feel about revealing the referee's name?

Dr. Powers replied that the decision to remain anonymous rested with the reviewer but that the editor has at times asked the reviewer if he were willing to enter into direct communication with the author.

THE BENEFITS OF CONSULTING ACTIVITIES TO A PHARMACEUTICAL CHEMISTRY TEACHER

Robert H. Miller

In the Talmud it is written that when the child is born the sons are to be carried high up into the mountain -- there to be kissed by the Angels. For it is further written, that if the Angels kissed them on their hands they may become a great painter, or if the Angels kissed them on their lips they may become a great singer. I have no idea on what part of Dr. Jannke's anatomy the Angels kissed him, but I certainly do know this -- he makes a great chairman.

William Howard Taft once said, that the best kind of audience to address, is an audience that is intelligent and well-educated, -- but half tight. Since this audience has been, for five days, one of the best audiences that I have ever seen for the speakers, something has made up for the absence of the last element that the remark implies. I must think that it is the high spirit of the Pharmaceutical Chemistry Teachers of today.

INTRODUCTION

In discussing the benefits of consulting activities to a Pharmaceutical Chemistry Teacher, I am going to present data which will be of help to everyone, who is interested in this type of work. Since material about consultantships is not ordinarily common knowledge, but at the same time is very broad in scope, this immediately creates a dilemma concerning coverage. A dilemma somewhat analogous to the chorus girl's dilemma who was donning her costume for the late, late show before a relatively unknown audience. After due consideration she could not decide whether she should wear her hoop skirt, which covered the subject without touching it, or whether she should wear her Gee string which touched the subject without covering it. And my dilemma gets even more complex when I weigh the concensus of opinions I have collected this week from the many people in this group who have talked to me privately about consultantships. One thing is certain, the nature of consultantships and consulting in general is but very poorly understood. Like the chorus girl, I shall at least try to cover a couple of high points. The material that I am going to present today is, more or less from the shoulder. Much of it is drawn from my own personal experiences and while they may not have been the best experiences, they are, none the less, the only experiences I have ever had. No literature references will be cited, because it is my opinion that if the data is in the literature, it is public property; and, as such, it is just as readily available to you as it is to me.

CONSULTING -- A NEW DEFINITION

First off, I have been requested to assume that I am speaking primarily with people that are not now engaged in consulting activities. Therefore, I would like to give you my definition and impressions of consulting and what one can expect from consultantships. As far as I can see, consulting is simply an additional opportunity of a very special nature to study and hopefully, to learn a great deal. Consulting is a very unique

opportunity too. It's a unique opportunity that allows you to acquire information and knowledge that is frequently of a very highly confidential nature. And hence, as such, it embodies a very special trust. This is as Dr. Hartung and Dr. Burckhalter so impressively stated earlier this morning. Thus consulting is another one of those extending educational opportunities because consulting can potentially act to create a far better informed teacher. Now I didn't say a far better teacher, I said a far better informed teacher because, literally, consulting work becomes a demand situation. It is a demand situation to further your own personal education in both the theoretical and practical areas that happen to be concerned in your particular consulting contract. Now if you have basic teaching abilities, consulting activities should add a great deal to you as a teacher. Collectively, all this should rapidly pyramid where it is more important, in advantages to the student and to the student's satisfaction.

GENERAL BENEFITS OF CONSULTING ACTIVITIES

What are some of the general benefits of consulting activities? I am sure, from the many private conversations of the last week that the general benefits of consulting are very well recognized by all but a few diehard administrators. But the fears of the die-hard administrators are not pure hog wash, because a consultantship can easily be abused and get out of hand, which frequently happens. More about that if time permits! It seems to me that one of the most important advantages of a consultantship is that it takes one out of the cloistered halls of the ivory tower and as such it certainly gives me, and I assume everyone else a much truer realization of the rough economic world in which we live -- a world of keen competition! In consulting, one is inadvertently in contact with current marketing problems which are always sobering thoughts. From a very personal standpoint, one of the great benefits of consulting is, without a doubt, the esoteric effect. Esoteric is derived from a beautiful Greek word meaning inner, private or personal pleasure and esoteric thus denotes that warm inner feeling that comes from doing a reasonably good job on a consultantship. Another benefit -- consulting tends to improve ones self confidence because it throws you in contact with different types of people in many different strata of life and this has an extremely tempering effect upon one's thinking processes. A further general benefit of consulting is that it brings you in contact with a large number of industrial plants and as such it acts as an entree into a host of industrial plants which you could not ordinarily enter or study. For example, Dr. Robert Brasted who is a consultant for Olin Mathieson and a member of the staff of the Department of Inorganic Chemistry at this University has repeatedly told me that he has learned far more inorganic chemistry in his consulting capacities than he could possibly have had the opportunity to learn had he restricted his activities to University teaching. He feels that his consulting has given him a much firmer grasp of the overall field of inorganic chemistry. Still another important benefit of consulting is that it creates the opportunity to see confidential research and marketing reports and consequently one knows what research avenues are being pursued in the particular company concerned. Frequently one also acquires a reasonably good knowledge of what is being done in the entire and related industries as well. Industry has its ear to the ground! From a general standpoint consulting also provides an opportunity to learn a great deal about organizational and management procedures -- how they operate and perhaps even more important, how to circumvent them.

You may say to me that some of the general benefits of consulting activities are largely of limited value because one cannot speak freely about the specific data or research problems with which you are directly or indirectly concerned. This may be partially true, but in a consulting capacity one is usually dealing with confidential material and thus one knows something quite special about the direct future of the world other than the confusions and frustrations which appear daily in the newspapers.

A further great benefit of consulting for a large firm is the immediate availability of the firm's abstracting and library services. The value of this great asset needs no further expansion.

There are also other general benefits of consultantships that are of an esthetic nature. For example the increased respect and prestige of the students toward their instructors that are so engaged. This prestige tends to enhance the pride of the student in his school and his instruction. This tends to challenge the infamous Shaw adage "They that can, do - they that can't, teach". Another esthetic effect associated with consulting is the general elevation of the College and the all University prestige derived from the specific staff member who is consulting for a good progressive concern. This further tends to elevate every faculty member by the simple process of association.

A final general benefit of consulting activities to Pharmaceutical Chemistry Teachers is the opportunity to serve the people of the state, of the nation and of one's own University. To illustrate, let me cite the University of Minnesota Creed:

> Founded in the Faith that men are ennobled by Understanding
> Dedicated to the Advancement of Learning and the search for truth
> Devoted to the Instruction of Youth and the Welfare of the State

SPECIFIC BENEFITS OF CONSULTING

If we turn now to the more specific benefits of consulting activities it is immediately obvious that such benefits come in great clusters - like grapes or in bushels like wheat. These specific benefits obviously depend upon the particular area in which you are doing the consulting. You might, for example, learn a great deal about modern drug formulae and modern drug formulation. You might have an opportunity to learn a great deal about new materials and the formulation of new materials and perhaps, the chemistry of new materials. The same could be true of the pharmacology of new materials. You could have a much greater opportunity to learn about new and unique laboratory techniques. This is particularly true if you are consulting for a large firm which ordinarily has costly new equipment available in a relatively short period of time. You may also learn a great deal about organization and operation of various research laboratories. You may learn first hand about clinical testing; types, methods, adaptations, etc.; development of facilities; development of controls; product and patent laws; product trade marks; labels and labeling; packaging and storage; F.D.A. regulations; new drug applications; drug certification; biological development and control; product development; promotion; marketing; advertising; or whatever it may be that has to do with the specific area in which you are consulting; and therefore many, many more areas and topics than we have quickly listed. I have left for last what I believe is the most important specific advantage of consulting activities and I have left it until last because I am using the

Aristotle system which climaxes with the most important point. It seems to me that the biggest specific advantage of consulting for a good sized firm is that it makes available grants, funds, and other aids for University research. Other aids, what might these be? Perhaps pharmacological testing! All of you, I am sure, are aware of the questionable value of pharmacological testing that has been done in a host of laboratories using varying techniques when a simple duplication of procedures is often extremely difficult to say nothing of the complexities of extensive data correlation. There are also many other direct aids such as carbon-hydrogen analysis, nitrogen determinations, methoxy values, infra-red and ultra-violet tracings and many, many other specific aids. I would like to emphasize the point of funds, grants and other aids for University research. You can undoubtedly think of as many or more aids than I, so I want to stress this point by a special short pause to give you additional time to reflect. It seems to me that this is the most important specific advantage of consulting for Pharmaceutical Chemistry Teachers.

What then is the state of recognition of these general and specific benefits of consulting activities? It is generally agreed that the varied benefits are highly desirable, but I hasten to point out immediately that consulting is a privilege, it is not a right; and therefore, it cannot be taken lightly because it is so very easily abused. As a result of this, most large universities require a formal application to do consulting work. This must be approved by that magic thing called the Dean, by the President and by the Board of Regents. Consulting applications are not usually approved if it is known that they are intended for ordinary routine work, normally reserved for laboratory technicians even if such work is of some research value.

PURPOSES OF CONSULTANTS SERVICE

Perhaps it may benefit you as a Pharmaceutical Chemistry Teacher to realize the purpose of consultantships from an industrial standpoint. From an industrial standpoint, the purpose of consultantships takes a variety of twists. First, consultants may be used to solve a particular problem. This is ordinarily confined to a small company without adequate research and/or without control laboratories. You can think of many such examples. The elimination of rapid separation or sedimentation in a liquid would be a simple case in point. Many such problems occur in the early phases of marketing a specific product. Second, the industrial utilization of consultantships to seek advice on a major research project! Since we were 35 minutes behind schedule in starting this talk and lunch is soon due I shall forsake examples of such work in order to skip along more rapidly. A third use of industrial consultants is to suggest new ideas and/or new products. A fourth purpose for the industrial use of consultants is to see things through different eyes or from different viewpoints. I can perhaps best illustrate this by telling you about Michael Morarity, who had been having a series of financial difficulties. Further complications resulted because he had been hitting the bottle a little on the heavy side, and the pressure was on at home. Michael staggered into church one Sunday morning just as Father O'Halloran said, "If you have any difficulty, trouble or strife, just call upon God, because God is always ready to help you". Well, as Michael thought it over, there was no question but what he could use some help, so he sat down and wrote an explanitory letter to God which concluded as follows, "God, if

you can see your way clear to send me a hundred dollars, I certainly would be most grateful because I can use it". He folded the letter, placed it in an envelope and began to address it. In short, he put a G on the envelope and then thought, "This is going to look a little peculiar directing a letter to God through the postal system". Thus he decided to simply circle the G and reasoned God is omni-present and omni-intelligent, let him solve this delivery problem. When the letter reached a sorting clerk, he turned to a second clerk and said, "Hey Joe, what's this?", Joe took a look and said, "I don't know, give it to the foreman". So he gave it to the foreman, who in turn passed it to the inspector. He said, "I'll take that letter, I think I know where it goes". The assistant postmaster, varified the inspector's opinion by saying, "Sure there's the G with the circle around it, that's supposed to go up to the Masonic Lodge, that's a Masonic symbol." At a subsequent meeting of that Masonic Lodge the secretary reported and read Michael Moriarity's unusual correspondence. Ultimately, the group decided that, while Michael Morarity was not a member, the Masons were basically a philanthropic organization, so let's give Mike a little help. We won't send him $100, but we'll send him $50. This they did! The very next lodge meeting there was another letter addressed in essentially the same way from Michael Morarity which read, "Dear God, I want to thank you for the prompt manner in which you dispatched my request for funds, but God let me tip you off to one thing. The next time you send me any money, send it through the Knights of Columbus; those damn Masons kept half." Thus you see, one of the truly great advantages to management of consultant service is to obtain various viewpoints; just as Michael saw his problem through somewhat different eyes than one would normally expect. There have been many examples of the value of this wisdom. Shakespeare in Macbeth is frequently and erroneously credited with the old German proverb, that is so often used to express this problem i.e. "You don't see the forest for the trees".

One of the most important purposes of consultant service however, especially from an industrial standpoint, is to take management off the hook. This is not one of those things you see written, but rather is an insight into the internal politics of a particular company. Obviously, management does not state that a consultant is being obtained to take themselves off the hook, but just that frequently happens. You must remember that in a large industrial concern, a memo from the head office is ordinarily treated just as if it were a stone tablet direct from Mount Sinai. This is in sharp contrast to a University where wastepaper baskets receive their more proper use. Let me cite an exact memo that was handed down from the head office of a large corporation in this country. Many of you may have stock in this company. "You men who originate our products are the chaps who are supposed to keep the smoke coming out of the factory chimney. The volume of smoke emmitted from our chimney during the past six months hasn't been large enough to darken the landscape to any great extent. Now that the "dog days" are over and the business revival period has begun, we are addressing to you a short, sharp request on this subject. We want more smoke and we want it now." Remember, in a large industrial organization, it is physiologically inescapable that when you step on the cat's paw the sensation of pain is transmitted to the cat. Also remember that the personnel of top management are the high priests in the temple and they want to stay in the temple. If the high priests lose faith, the temple walls start to crumble. It is imperative that you remember this, if you want to be invited back.

There are many neurotics and many psychotics in the business world just as in any other world. Business administrators are frequently under a lot of pressure. I am sure that all of you know that a neurotic is an individual who builds castles in the air. A psychotic is an individual that lives in these castles and a psychiatrist is a person that charges both of them rent. One more tip about management! Consulting work frequently represents dealing with management directly or indirectly. Frankly, this means using the art of plain talk. This means using three syllable words when three syllable words should be used. It also means avoiding strange words and ten syllable words when three syllable words will do. The lack of the art of plain talk creates dislikes and most people are more conscious of their dislikes then of their sympathies. The latter are weak while the hatreds are strong. It is one of the humiliating features of human nature that we resent a few little things which happen to irritate us more than we appreciate a great deal for which we ought to be grateful.

TYPES OF CONSULTANTSHIPS AVAILABLE.

Perhaps it might be a benefit to you as a Pharmaceutical Chemist, to have some knowledge as to what type of consultantships are available in industrial concerns. First off, they are very highly varied and they are in all scientific areas. This means there is a place in the sun for everyone, but the sun sometimes gets very hot. In the business and economic world there are also consultantships of all types available and I cite for you an article in the Wall Street Journal, May 8, 1958 entitled "Corporate SOS, More Companies Seek Consulting Advice in Combating Recession". There are also many other consultantships available that are neither of a business nor of the strictly scientific nature. For example, there is considerable use of psychology in business procedure today. Many of you know that just as a magician pulls a rabbit out of a hat, a psychologist pulls a habit out of a rat. There are many other types of consultantships that are available too. I can best illustrate this by telling you about Mr. Brown's Tom Cat named Rhubarb who was catting around evey night and creating an awful lot of confusion while pacing the top fence rail, howling like mad, and keeping everyone in the neighborhood awake. Finally the neighbors got together and decided the tom cat has got to go! Since these neighbors issued their statement in the form of an ultimatum Mr. Brown took Rhubarb to a modern veterinarian where surgery was performed under "pentothal". In no time at all the cat was home. The surgery was successful and the post operative recovery was complete; but Rhubarb would not stay home! Rhubarb promptly revived his nocturnal activities which precipitated a second War Council in Rhubarb's name. Mr. Brown was again confronted with angry neighbors demanding an explanation. Mr. Brown replied that "Rhubarb was not catting around, he was merely out nights acting as a consultant". So you see there are several types of consultants; consultants who can actually do the job or perform the work themselves, and other consultants who merely consult or tell how the job should be properly done!

Incidentally, the food packaging industry has made great advancements in the last few years, and modern food packaging, utilizing new techniques and new materials, is rapidly gaining in scientific and technical complexity. I can tell you from personal experience that modern food packaging embodies a tremendous number of chemical problems which Pharmaceutical Chemists are especially well qualified to solve. This is a special area that I would like to direct to the attention of anyone seeking consulting work.

INDUSTRIAL UTILIZATION OF CONSULTANTS

Perhaps it would benefit you as a Pharmaceutical Chemistry Teacher to understand how consultants are utilized by industry. For one thing, and this is by far the roughest thing that happens, a consultant gets involved in interview type visits with key personnel. This means that you are at the mercy of the various administrators or heads of departments. These various administrators proceed to ask a whole host of questions that they themselves can't answer. Will this product or development be a success -- if we market it? What is the potential market? And a whole host of other questions of that nature! In this interview the consultant is involved with all types of personnel in administrative capacity and he may be expected to span the arc from highly scientific questions to advertising and promotion inquiries. This is rough treatment, and at the end of the day, you really feel as if you've been dragged through the mill. You know that whatever is your consulting fee; its not enough!

The other extreme from the interview technique is far less trying. This is participation in group discussions; a type of round table technique in which the consultant appears to act as a sounding board. The consultant's principle function is to listen. In other words he's a "good conversationalist"! The consultant acts as a catalyst to induce the other individuals at the round table to discuss their work among themselves for new ideas, new products, or for product improvement. This is a mechanism which is largely used to improve morale and to get the research workers speaking among themselves once again.

A third and very important use of a consultant from the industrial standpoint is to induce personnel, especially research personnel, to separate the qualitative aspects of a problem from the quantitative ones. This is something that research workers do not ordinarily like to do. They prefer to work on the quantitative aspects. From an industrial standpoint this is not desirable and may entail much unnecessary expense. Therefore, an effort is made through consultants to induce personnel to separate the qualitative aspects of the problem from the quantitative one and then to concentrate on solving the qualitative aspects first. This is much more economical and ultimately the quantitative aspects may or may not have to be solved. This is completely irrespective of whether the product or the project is abandoned or salvaged. From an industrial standpoint negative answers are a warning to save much expensive work.

Another way in which a consultant is utilized by industry is to act as a coordinator between various research groups and/or management. Research personnel and management do not ordinarily speak the same language. This barrier creates communication problems. In such cases a consultant acts as a buffer between the groups. This is an area in which many consultantships are available.

Another industrial method of utilizing consultants is to actually solicit them to suggest or map out a course of action for management to pursue in their particular research organization. This is frequently done to spread the basic structure of a company and thus render it less vulnerable to cyclical economic factors.

DANGERS OF CONSULTANTSHIPS

I hasten to say in defense of the Deans (and how I hate to defend them) there are dangers to consultantships. Unfortunately, arrangements whereby a professor is permitted to do outside consulting work frequently deteriorate to the point where the academic positions become secondary. This is especially true with small concerns who have little or no library and/or laboratory facilities. These petty type consultants are soon using the Universities time and the Universities equipment to do library or petty laboratory work on petty problems. This obviously challenges academic freedom and is highly undesirable!

A further danger inherent in consultantships is the occasional request to write up some sort of endorsement or substantiation of data. This is particularly true if the nature of the problem is such that the confidence limits of the work are but poorly defined. You just can't say this is good or it is bad! In this situation a consultant may be confronted with a request for a favorable written or oral report. A common procedure repeatedly utilized to accomplish this end, is for company management, in the form of a high administrator, to wrap up their product (which John Litchfield of American Cyanimid, calls "Neopup" or "Super Neopup") into a vicuna coat and have the consultant stay for a few days in a Boston Hotel; all expenses paid. Then the consultant maybe requested to tell management what he thinks of "Neopup". Obviously the individual integrity is at stake here and this becomes a great pitfall if the consultant is weak. Some managements would like to say that such and such an individual of such and such a university states that this product is excellent.

Another great danger is the lack of knowledge of the effect of placebo drugs! It has been definitely established that a placebo drug given by an administrator in whom the patient has confidence may result in dramatic patient improvement and also favorable alteration of the patient's blood chemistry. This may come as a distinct shock! It did to me, in spite of the fact, that I was reasonably familiar with the very powerful physiological basis of faith healing. It is very important that you insist on double blind collection of data.

A very common industrial pitfall is perhaps best described by the term "Parkinson's Law". Many of you may have read the very popular and entertaining book by Professor C. Northcote Parkinson entitled "Parkinson's Law or Other Studies on Administration". If not I would strongly suggest that you do! Parkinson humorously shows statistically that the number of enemy that are killed in the field varies inversely with the number of generals in your own army. Parkinson is, of course, referring to the rapidly growing and complicated problem of administration and communications. I also suggest that you also read the publication "Crashing the Communication Barrier" by William Oncken, Jr. published on page 72 of the 1956 Midyear proceedings of the American Pharmaceutical Manufacturer's Association. Oncken forcefully points out that good communications does not consist in the useless passing of worthless papers up and down the lines of an administrative organization chart.

INDUSTRIAL PROCEDURE FOR CONTACTING CONSULTANTS

What are the procedures that are utilized by industry for acquiring consultants? This may be of significant advantage to you, but since we are very short of time I can only briefly mention a few techniques. Let me point out to you that from an industrial standpoint many people are called for a consultantship but few are chosen; and most people do not even know that they have been called! The Seminar method is widely used. A potential consultant candidate is invited to present a Seminar at the particular industrial firm that is interested in his services. He may be invited as the guest speaker at some special meeting where officials of this interested company were influential in suggesting the name of the guest speaker. Confidential reports are used by industry and many such reporting services are available. Finally, informal luncheon meetings are widely used to contact a potential consultant.

INDUSTRY COMPENSATIONS OF CONSULTANTS

Without going into detail since we are short of time, it might be of benefit and interest to you as a Pharmaceutical Chemistry Teacher, to know how salaries of consultants are determined. Obviously supply and demand are important factors in determining the salary of consultants. The quality of one's bargaining power is also important. The above factors are particularly valid in dealing with relatively small companies that have no established consulting policy. However, with a large company the consulting policy is ordinarily rather well established and an equitable system is normally employed to arrive at the consulting fee. Normally your monthly salary at the University is divided by the number of working days in the month and to this figure an additional 20% fee is usually added. Any incurred expenses are independent of this fee. But let me caution you, you cannot say, "Now I am a consultant, I want a $100 per day". There are two serious extremes to be considered. In the 28th proverb there is a timely statement which reads, "He who maketh haste to be wealthy shall not be innocent". On the other hand, it is a very serious mistake to set consulting fees too low. In this latter situation you become a subscriber to that solemn reverence of the money-worshipers, who believe that grim dogma "that the golden coins are only for him who has grubbed them out a penny at a time". In a tempering vain let me say this! If as some educators think there is something wrong with making money then there is something wrong with our whole way of life.

We have talked of many things and if in summary we cast the cold blue analytical lights on the benefits of consulting activities to Pharmaceutical Chemistry Teachers these lights are, in fact, not cold and blue at all; but rather are very bright, glowingly warm, and soothing - like a "dram of drambuie". As such consulting service is a fitting finish to a fine feast. But before you jump, I urge <u>great</u> caution in accepting and in handling any consultantship because consulting is work and only by caution will the intellectual reward be truly stimulating. Be cautious in accepting consultantships! There are many available; don't grab at the first one that comes along. Be cautious like the farmer whose barn burned completely down to the ground. The barn was insured for $15,000 and it could not be replaced for that price. As a result the adjuster insisted that the insurance company was going to duplicate the barn exactly

as it was before the fire. Since farming methods have changed and the barn had been of limited value the farmer was much more interested in the $15,000 cash settlement. After a lengthly discussion in which the farmer was insisting on a cash settlement and the insurance agent was insisting on exactly duplicating the barn, the farmer rose in disgust and said, "All right, if that's the way you are going to do business, you can cancel the life insurance on my wife".

I thank you.

BIOLOGICAL VARIATION IN DRUG METABOLISM

Bernard B. Brodie

There are many factors which limit the duration of action of a drug but today I shall discuss only one of these -- biochemical inactivation in the body. We often think of drug action as being terminated by the combined effects of urinary excretion and metabolic transformation. In recent years, however, it has become more and more evident that for most drugs urinary excretion is of relatively minor importance in limiting drug action, and most drugs must undergo chemical modification before they can be excreted by the kidney in more than minor amounts. Without biochemical mechanisms for the metabolism of foreign compounds, much of present day drug therapy would be impractical since most drugs would act for too long a time. In addition, treatments for poisoning by many toxic organic compounds would be almost hopeless. But important as these mechanisms are in drug therapy, their variability from species to species and from person to person, creates difficulties for the pharmacologist in screening compounds and for the clinician in treating patients.

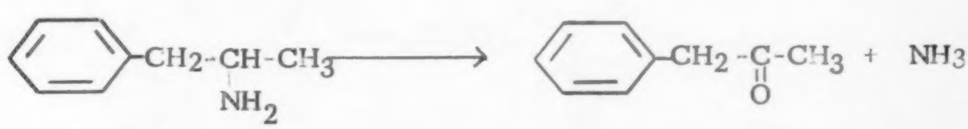
A great deal of work on the metabolism of drugs in the body has led to the surprising conclusion that most drugs are metabolized along a surprisingly few chemical pathways.

I shall briefly summarize the more important of these reactions.

Oxidation by Enzyme Systems in Liver Microsomes

Many drugs are oxidized in liver microsomes by enzyme systems which have the unusual requirement of both TPNH and oxygen.

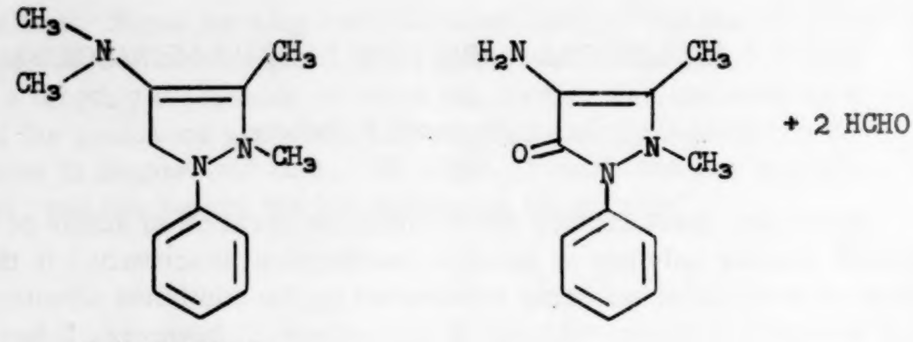
Deamination



Amphetamine

This reaction is of historical interest since it was the first of the microsomal reactions to be studied. It is catalyzed by a deaminase, which differs from monoamine oxidase, since it does not attack the usual monoamine substrates, e.g., norepinephrine or serotonin. It is surprising that the enzyme is present in rabbit microsomes but is absent from a number of other mammalian species. Accordingly amphetamine does not undergo deamination in man and dog but is hydroxylated in the para position.

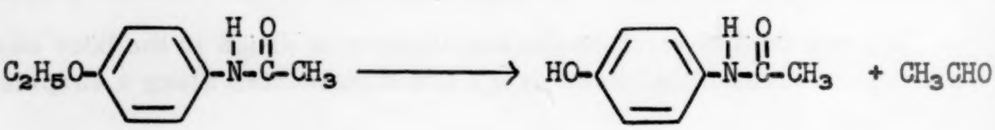
N-Dealkylation



Aminopyrine

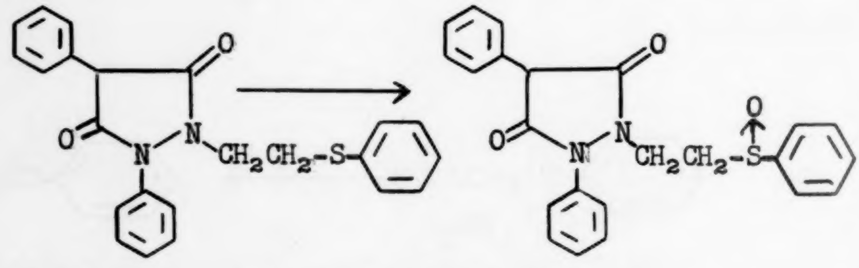
This rather common reaction in drug metabolism removes N-alkyl groups from alkylamines to yield an amine and an aldehyde. The present evidence suggests that at least two different enzyme systems are involved in N-dealkylation, for example, the methyl group is removed by a different system from that which removes higher alkyl groups.

O-Dealkylation



In this reaction, O-alkyl groups are removed from ethers to yield a phenol and an aldehyde. Here also there is evidence for more than one enzyme system. For example, p-ethoxyacetanilide and codeine are demethylated by different enzymes.

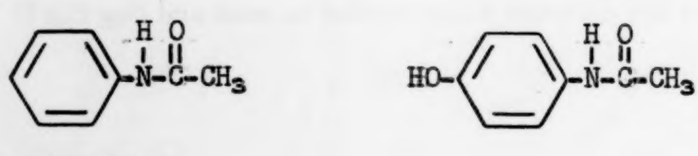
Sulfoxide Formation



4-(Phenylthioethyl)-1,2-diphenyl-3,5-pyrazolidinedione

Thioethers, instead of undergoing dealkylation, are oxidized to the corresponding sulfoxide. Chlorpromazine, a phenothiazine derivative, also forms a sulfoxide as its main metabolic product.

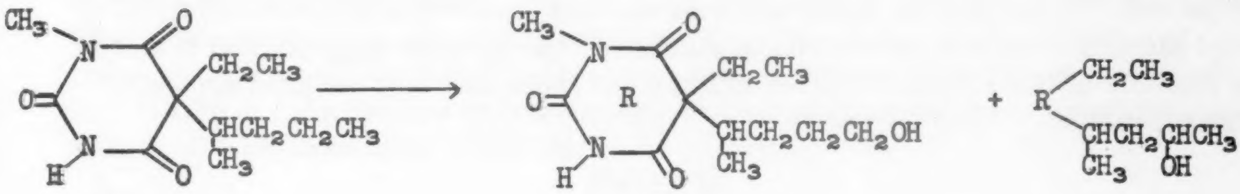
Hydroxylation



Acetanilide

Many aromatic structures are converted to phenolic compounds. Recent studies indicate that different enzymes may be required for ortho, meta and para substitution.

Sidechain Oxidation



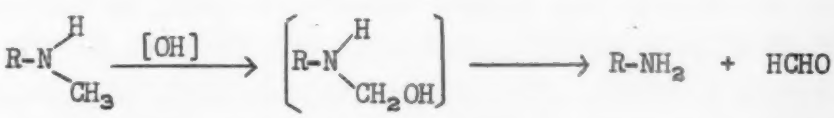
Hexobarbital

Barbiturates and other drugs with alkyl sidechains are inactivated by sidechain oxidation. The oxidation of pentobarbital and thiopental occurs at both terminal and penultimate carbon atoms, the reactions being catalyzed by different enzymes. The primary alcohols formed by oxidation at the terminal atom undergo further oxidation to carboxylic acids by the action of enzymes in soluble fraction of the cell.

General

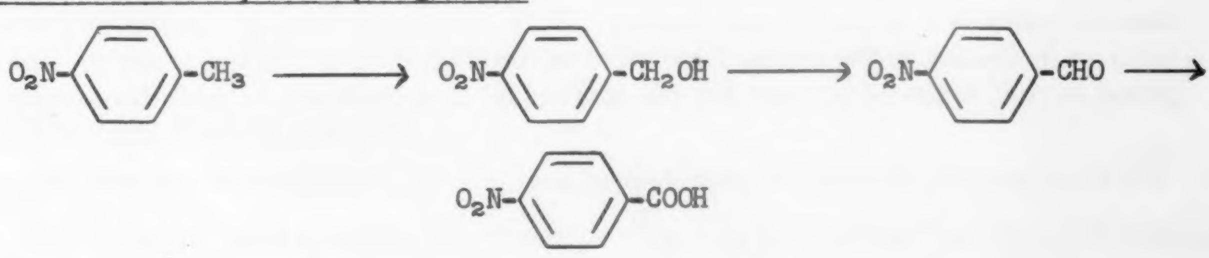
A number of oxidative enzyme systems have been grouped together because they have certain properties in common. They are all in microsomes and have the anomalous requirements of both TPNH and oxygen.

Most substrates in the body are oxidized by the action of dehydrogenase enzymes. In many of these reactions TPN is a hydrogen acceptor. But in these microsomal reactions the TPN is already in a reduced condition, yet it participates in oxidative reactions. This odd combination of requirements is now appearing in other types of reactions, for example in hydroxylation of steroid rings. Present evidence suggests that TPNH reacts with O_2 and some unknown microsomal substrate to form an intermediate "hydroxy" donor which in conjunction with certain non-specific catalysts transfers a hydroxy group to the drug substrate. Accordingly, dealkylation of an alkylamine might be written.



Other Types of Oxidation

Alcohol and Aldehyde Dehydrogenases

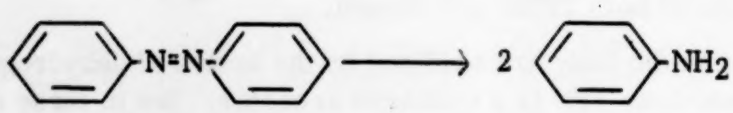


Alcohol and aldehyde dehydrogenase are important in metabolism of foreign compounds which form alcohols or aldehydes as intermediates. Thus, p-nitrotoluene is oxidized to the alcohol by a TPNH dependent enzyme system in liver microsomes. The alcohol is then oxidized successively to the aldehyde and the acid by the action of DPN dependent alcohol and aldehyde dehydrogenase located in the soluble fraction of the cell. These are the same enzymes that are involved in the metabolism of ethyl alcohol. The non-specificity of alcohol dehydrogenase suggests that it should be possible to find inhibitors of the enzyme and make that lost weekend somewhat less expensive.

Reduction

Some drugs undergo reduction in the body. Two enzymes that have been studied in detail are nitro reductase and azo reductase.

p-Nitrobenzoic Acid



Azobenzene

These reactions occur mainly in liver and are catalyzed by flavoproteins which require TPNH as a hydrogen donor. Surprisingly enough, the two enzyme systems are different and can be separated by ammonium sulfate fractionation. Azo reductase is active under aerobic conditions and is consequently an active enzyme _in vivo_. In fact, without this enzyme the sulfonamides would not have been discovered when they were, for the azo reductase enzyme converts Prontosil, an inactive antibacterial compound _in vitro_, to an active compound, sulfanilamide, _in vivo_.

Nitro reductase is not very active in the presence of oxygen and so does not play much of a role in the metabolism of nitro compounds. Many studies in literature indicate that the reduction of nitro compounds is an important reaction but this conclusion is based on studies of orally administered drugs. Microorganisms in the intestine have a different nitro reductase that reduces nitro compounds aerobically or anaerobically in a very efficient manner. This enzyme is very important to the bacteria as reduction to the amino derivative is the first step in ripping apart the compound so that it can be utilized for the nutritional requirements of the microorganism.

Conjugation

Glucuronide Formation

The last few years have seen the complete elucidation of the mechanism of glucuronide formation. This reaction is important in the metabolism of phenols, alcohols and carboxylic acids. Recently the formation of norepinephrine and serotonin glucuronides has also been reported. Enzymes in the soluble fraction of liver produce an active form of glucuronic acid -- uridine diphosphate glucuronic acid (UDPGA). An enzyme in liver microsomes catalyzes the transfer of glucuronyl acid from UDPGA to drug substrate.

$$\text{UDPGA} + \text{phenol} \longrightarrow \text{phenyl glucuronide}$$

Of considerable interest is the inability of cats to form glucuronides.

Sulfate Conjugation

This pathway also involves conjugation with phenols. The first step is the formation in the soluble fraction of the liver cell, of an active form of sulfate:

3' - phosphoadenosine - 5' - phosphosulfate (PAPS)

An enzyme also present in the soluble fraction transfers sulfate from PAPS to a phenol:

$$\text{Phenol} + \text{PAPS} \longrightarrow \text{phenylsulfate}$$

Acylation

Acylation involves conjugation of a carboxylic acid and an amine, either of which may be the foreign compound. Thus with sulfonamides and other foreign amines

$$\text{Acetyl - CoA} + \text{sulfanilamide} \longrightarrow \text{acetylsulfanilamide}$$

the catalyst is present in liver and kidney mitochondria.

It was the study of the acetylation of sulfonamides that led to the discovery by Lipman of the activated two carbon fragment acetyl - Co. Though this reaction is common for the metabolism of primary amines, dogs do not have the mechanism. Foreign compounds like benzoic and phenylacetic also form active CoA derivatives. The acyl radical is then transferred to glycine by the action of an enzyme in kidney and liver mitochondria.

$$\text{Benzoyl CoA} + \text{glycine} \longrightarrow \text{hippuric acid}$$

Mercapturic Acid Conjugation

Aromatic compounds are metabolized to mercapturic acids in several ways (1):

(a) A labile nitro group on the aromatic ring may be replaced by an acetylcysteinyl group.

Pentachloronitrobenzene ⟶ N-acetyl-S-(pentachlorobenzyl) cysteine

(b) An active halogen on an aromatic ring or an alkyl sidechain may be replaced.

Benzylchloride ⟶ N-acetyl-S-benzylcysteine

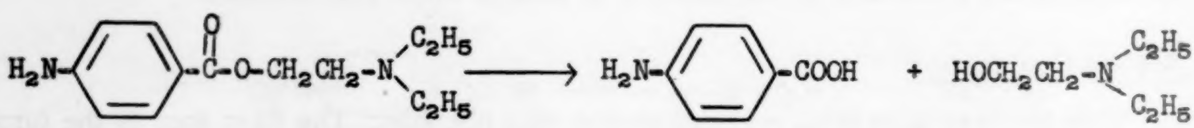
(c) A nuclear hydrogen atom on an aromatic ring may be replaced.

Naphthalene ⟶ N-acetyl-S-(naphthyl) cysteine

The enzymatic mechanisms are not yet known. Apparently, cysteine is introduced by a peptide donor after which acetylation occurs.

Hydrolysis

De-esterification



Procaine

The last reaction to be discussed is deceptively simple. Procaine and a number of esters are hydrolyzed by the action of a plasma esterase. Other esters, like Demerol, are split by an esterase in liver microsomes. Apparently there are a whole galaxy of hydrolytic enzymes whose specificities still to be described. But one interesting peculiarity is the hydrolytic enzyme in rabbit plasma which acts on atropine and thus enables him to eat all the belladonna leaves he likes.

Biological Variations

Having touched on the important enzymes that metabolize drugs, I shall now discuss the important problem of biological variation. In attempting to produce new and better therapeutic agents, the pharmacologist inevitably faces this problem, since he must decide on the basis of animal experiments which drugs are worth a therapeutic trial in man.

Some species differences in drug action are purely qualitative. Morphine, for example, depresses man but stimulates cats and racehorses. Most species differences, however, are in duration of drug action, and result from species variation in rate of metabolic inactivation.

A few examples taken from our own experiences will illustrate the extraordinary difficulties in extrapolating results obtained in animals to man and vice versa. In studying the physiological disposition of meperidine (Demerol) we gave a dog an enormous dose of the narcotic -- 20 mg per kg intravenously. In full expectation of dire respiratory depression, we gathered together all the paraphernalia, including the resident anesthesiologist, to furnish artificial respiration. At the end of the 20

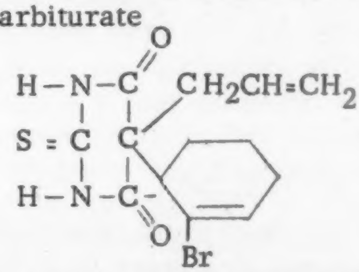
minute period of drug infusion, I could almost swear that the dog winked at me, scrambled off the table and calmly sauntered away. After recovering from our surprise we found that the narcotic was destroyed in the dog at the extraordinarily rapid rate of about 90 per cent per hour, compared to about 15 per cent per hour in man.

The next example represents serendipity at its best. Phenylbutazone (butazolidin) is a potent non-steroidal antirheumatic drug, a pyrazolone derivative, which is metabolized slowly in man, about 15 per cent per day. In rats, mice, guinea pigs, rabbits, dogs and horses, the drug is metabolized completely within a few hours. If you ask me why we included a horse, and a thoroughbred at that, it is simply that even upper class horses have arthritis and this particular horse was under treatment for the ailment. It is not surprising that the anti-rheumetic action was first observed in man since it is so rapidly metabolized in other species that enormous doses are required to produce an anti-inflammatory effect.

The story of how the drug was discovered is an interesting one. Someone had the idea that the old standby pyramidon (aminopyrine) if given intravenously in big enough dose might have an anti-arthritic effect. But how to get large amounts into solution was a perplexing problem. It was remembered that sitting on the shelf was phenylbutazone, an acid pyrazolone, while pyramidon was a basic pyrazolone. Why not put the two together to form a complex which would be highly soluble? The combination was highly successful as an anti-arthritic agent, in fact so much so that a suspicion arose that the solvent factor phenylbutazone was the only active drug, and so it proved.

Ethyl biscoumacetate (Tromexan) was introduced as an anticoagulant in an attempt to develop an agent more rapidly inactivated than Dicumarol since the long duration of the latter compound adds to the danger of bleeding tendencies. Tromexan was developed from studies using rabbits, which metabolize Tromexan at the same rate as man. However, this similarity is a sheer coincidence since the pathways of metabolism in the two species are completely different. Ethyl biscoumacetate is enzymatically inactivated in man by hydroxylation of the aromatic ring, and in the rabbit by de-esterification. In contrast to this, the dog inactivates this drug by the same chemical reaction as does man, but so slowly that screening in dogs might well have led to its being discarded.

A final example represents a personal experience in frustration. For years we had been trying to develop a barbiturate that disappeared rapidly from the body. Such a compound could be of great value to the dentist for example, so that patients would not have to leave the dentist office still full of barbiturate. A long and ardous screening program finally turned up a thiobarbiturate



that elicited deep anesthesia yet was metabolized extremely rapidly in dogs. But when hopefully the compound was administered to man it was proved to be the most stable

barbiturate we had ever studied. The screening program came to a close since no one was convinced that there was a big future in dog dentistry.

A systematic exploration of species differences in drug metabolism was made comparing the rates of metabolism of hexobarbital, antipyrine, and aniline in a number of species. Table 1 illustrates the striking species variation with the mouse metabolizing hexobarbital 20 times and antipyrine 60 times as rapidly as man. How many good drugs have been discarded because they showed little action in the mouse, only because this species metabolized them too rapidly?

A thorough study of the metabolism of hexobarbital shows that the wide species variation in response to this drug is largely due to differences in the rate of metabolism in vivo. We see an excellent correlation between "sleeping time" and the biologic half-life (Table II). Comparison of the duration of action of hexobarbital with its rate of oxidation by liver microsomes in vitro reveals an inverse relationship. Accordingly, it may be concluded that species variation in the duration of action of hexobarbital may be pinpointed to variability in the enzyme responsible for its metabolic breakdown.

Strain Differences

When drug response in man and mouse are compared, what mouse are we talking about? There are a number of inbred strains of mice which show widely different abilities to metabolize drugs. Hexobarbital, for example, is metabolized 400 per cent more rapidly in one strain than in another. Individual members of a given inbred strain show a remarkably uniform response, while the members of non-inbred strain show considerable variation. We cannot find any sort of a rule that fits mice in general but only a particular population of mice. Since the inbred strains all get the same diet, heredity must be an important factor in determining the rate of metabolism of drugs.

Sex Differences

It has long been known that there is something different between the sexes. In rats this is shown by an increased sensitivity of females to the action of a number of drugs. For example, when rats are given 100 mg per kg of hexobarbital, the females sleep about four times longer than the males. This longer sleeping time is the result of a slower rate of disappearance of the drug in vivo and a lower activity of the liver microsomal enzyme which metabolizes hexobarbital. This sex difference in rats is not apparent in the first month of life but appears as an increased activity of the enzyme system in the males at about the fifth week while the females remain constant. It is curious that other laboratory animals do not show sex differences in metabolism of drugs and fortunate for the physician that it is not evident in the human.

Variability in Drug Metabolism in Man

It is not surprising that in man there is such a pronounced variation in the rate of metabolism of and the response to a given drug, for compounds such as Tromexan and Dicumarol show as much as a tenfold variation in rates of metabolism in different individuals. This biochemical individuality is a major difficulty in drug therapy. A population curve of the rate of metabolism of a given drug would show a wide specrtum

of activity. In those with an extremely high inactivation rate the drug would show no effect. In those who metabolize it with great difficulty toxic manifestations would appear.

Why Drugs are Metabolized

Drug metabolizing enzymes differ from the enzymes of intermediary metabolism in so many ways that it is of interest to speculate on their origin. The reason why most drugs must undergo chemical modification before they are readily excreted becomes clear when the structure of the kidney is considered. Glomerular filtrate flows down tubules lined with epithelial cells, which appear to form a continuous membrane with lipoid characteristics. Most drugs are weak organic electrolytes and are passively reabsorbed as the lipid-soluble non-ionized moiety. For this reason, tubular reabsorption is virtually complete for many drugs. Lipid soluble drugs would remain in the body almost indefinitely unless the organism had a way of letting them escape into urine as less lipid-soluble derivatives. Perhaps then these enzymes were developed in the process of evolution to enable the animal to convert lipid soluble food impurities, the alkaloids, the terpenes, the steroids into more polar derivatives. The kidney is unable to excrete lipid soluble compounds, and so any such materials ingested along with the food would remain in the body of the animal. Unless some means were available for converting these compounds to an excretable form, their levels in the body would increase until they reached toxic values. A drug then may be similar to a class of foreign compounds to which the organism has been exposed over the ages.

In attempting to discover the origin of these non-specific enzyme systems, we studied drug metabolism in a number of lower forms of animals. The fish does not oxidize drugs nor do fish liver microsomes carry out the oxidative mechanisms of N- or O-dealkylation, hydroxylation, deamination, or sulfur oxidation which are common to mammals. However, the fish does not need to oxidize lipid soluble foreign compounds since they may be excreted unchanged through the gill membrane. Some frogs (R. pipiens and R. esculenta) and aquatic salamanders (S. necturus) are also unable to metabolize these foreign compounds, but rather excrete them unchanged through their skins, which are basically lipoid membranes.

Some species of frogs (R. clamitans and R. catesbiana) lead a more terrestrial life and have less permeable skins to protect them from dehydration. It was not surprising, therefore, to find that these animals did possess the oxidative enzyme systems, since presumably they are unable to readily excrete lipid soluble compounds through their skin. Terrestrial salamanders (A. maculatum) also possess the oxidative mechanisms, in sharp contrast to their aquatic counterparts.

On the basis of these results it seems likely that the oxidative disposal systems were developed in the transition of aquatic to terrestrial life. The early land-dwelling animals had to develop a means of conserving water -- and the scaly skin of the reptiles replaced the moist semi-permeable skin of the amphibia. With the development of a less permeable skin, however, another way of disposing of non-polar foreign compounds had to be found. The solution was the development of biochemical mechanisms to oxidize these foreign compounds to more polar derivatives which could be excreted by the

kidney. These enzymes were then passed on up the tree of evolution to the present day terrestrial vertebrates.

The conjugation of phenols with either glucuronic or sulfuric acids to form compounds excretable in the urine is another story of biochemical development. Fish are unable to conjugate foreign phenols in vivo, and as a consequence, are extraordinarily sensitive to these compounds. Amphibia, however, are capable of forming both glucuronides and sulfates, and these mechanisms are also present in higher vertebrates.

Animals did not evolve along only one pathway in their development from the original organism. Aquatic amphibia, for instance, developed a terrestrial offshoot, the toad. Studies with B. marinus have indicated that these animals (which have a rather impermeable skin) possess oxidative enzymes for disposing of non-polar foreign compounds. However, the mechanisms involved in these enzyme systems are different from those of the microsomal systems present in reptiles, birds and mammals.

Insects, which are terrestrial arthropods, would be expected to have the ability to metabolize lipid-soluble foreign compounds, since they, too, must conserve water. Indeed, many foreign compounds such as aminopyrine, hexobarbital, amphetamine and chlorpromazine are metabolized extremely rapidly by crickets (A. domestica) and grasshoppers (R. microptera). Semi-aquatic arthropods such as crayfish and lobsters also metabolize these compounds, but at much slower rates.

An interesting discovery is that the tadpoles of toads and frogs do not possess the oxidative drug enzyme systems, nor are they able to conjugate phenols. This is not surprising in view of the totally aquatic nature of their environment, and their permeable skins which permit lipid-soluble compounds free exchange with the surrounding medium. The aquatic larvae of terrestrial salamanders are also incapable of metabolizing non-polar foreign compounds. These results suggest that as these animals develop to the adult stage there is also a chemical metamorphosis which goes along with the physical changes taking place in the animal. This chemical metamorphosis results in the development of enzymes to oxidize foreign compounds.

In studying the drug enzymes, we have found that they seem to follow the edict, "ontogeny recapitulates phylogeny." In agreement with this, guinea pigs and mice at birth lack the oxidative drug enzymes. The enzymes begin to appear in the first week after birth. These results may very well explain some of the difficulties encountered in administering drugs to new-born babies. Thus, in the development of tadpoles to adult toads, and in the transformation of the mammalian foetus to the new-born baby animal we see a repetition of the aquatic to terrestrial conversion found in evolution. It is not surprising therefore to find the development of oxidative drug enzymes corresponding to the change in environment in these examples.

The story we have told on the evolution of the non-specific microsomal enzymes that oxidize foreign compounds is not unlike that which describes changes in nitrogen metabolism. In most aquatic animals, the end product of protein metabolism is ammonia, which, though toxic, is kept at a safe concentration by its rapid release to

the surrounding medium through semipermeable membranes. As a need for conservation of water arose, ammonia could not be excreted in this manner and the terrestrial animals developed enzymatic mechanisms to convert ammonia to the nontoxic urea or uric acid excreted in the limited amount of urine produced by the kidney.

It seems likely that an analogous situation exists for the oxidation of foreign compounds to more polar derivatives. A large number of these substances, present in food, would accumulate in the body to toxic levels through passive reabsorption in the kidney tubule unless the organism possessed mechanisms to dispose of them. Thus the development of the microsomal oxidative enzyme systems may be one of the biochemical adjustments which made possible the evolutionary emergence of animals from the sea.

Table I

SPECIES DIFFERENCE IN METABOLISM OF HEXOBARBITAL, ANTIPYRINE AND ANILINE

Figures in brackets refer to number of animals.

Species	Biologic Half-life in Minutes					
	Hexobarbital		Antipyrine		Aniline	
Mouse	19 ± 7	(12)	11 ± 0.25	(6)	35 ± 4	(6)
Rat	140 ± 54	(10)	141 ± 44	(6)	71 ± 1	(3)
Guinea Pig	--		110 ± 27	(5)	45 ± 8	(7)
Rabbit	60 ± 11	(9)	63 ± 10	(7)	35 ± 22	(6)
Dog	260 ± 20	(8)	107 ± 20	(8)	167 ± 66	(6)
Man	360		600		--	

Table II

SPECIES DIFFERENCE IN DURATION OF ACTION AND IN METABOLISM OF HEXOBARBITAL

Dose of barbiturate 100 mg/kg for mouse, rabbit, rat and 50 mg/kg for dog. Figures in brackets refer to number of animals.

Species		Duration of Action	Biologic Half-life	Plasma Level Hexobarbital on Awakening	Relative enzyme Activity
		minutes	minutes	microg./ml.	microg./gm./hr.
Mouse	(12)	12 ± 8	19 ± 7	89 ± 31	598 ± 184
Rabbit	(9)	49 ± 12	60 ± 11	57 ± 12	196 ± 28
Rat	(10)	90 ± 15	140 ± 54	64 ± 8	134 ± 51
Dog	(8)	315 ± 105	260 ± 20	19 ± 4	36 ± 30
Man			360	20	

STEREOCHEMISTRY AND MECHANISM OF ACTION OF SYNTHETIC ANALGISICS

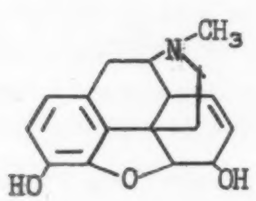
Arnold H. Beckett

INTRODUCTION

Stereochemical features of Analgesics.

A survey of the literature of analgesic compounds reveals the importance of stereochemical features in the biological action. Morphine (I) is the laevo isomer; its (+) isomer exhibits completely different pharmacological actions.

I



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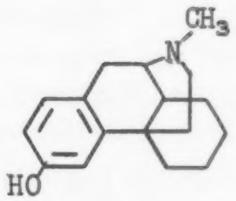
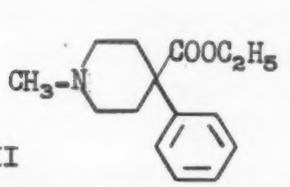


The analgesic activity of the morphinans resides in the (-)-isomer e.g. (-)-Dromoran (II) is a potent analgesic whereas the corresponding (+)-isomer is almost inactive.

The fortuitous discovery of pethidine (III)



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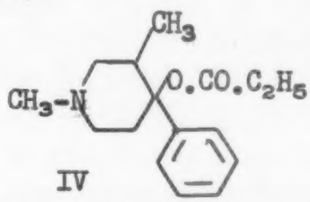
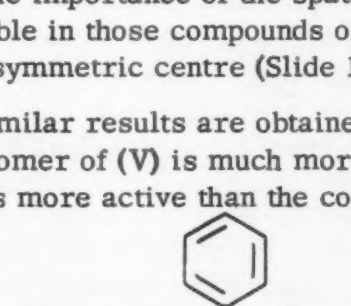


IV

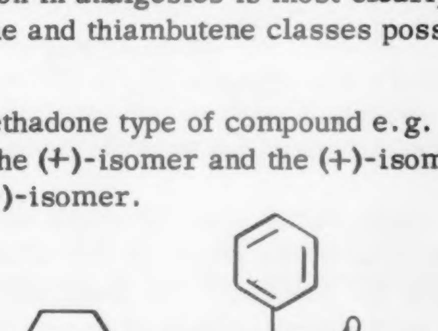
in 1939 commenced a new era in the search for analgesics. Soon the importance of stereoisomerism on the analgesic effect of this type of compound became apparent e.g. one diastereoisomer of the reversed ester of pethidine (IV) was more active than the other.

The importance of the spatial configuration in analgesics is most clearly discernable in those compounds of the methadone and thiambutene classes possessing one asymmetric centre (Slide 1).

Similar results are obtained in the isomethadone type of compound e.g. the (-)-isomer of (V) is much more active than the (+)-isomer and the (+)-isomer of (VI) is more active than the corresponding (-)-isomer.



V



VI

Importance of the N-alkyl group.

In this brief survey of analgesics, a further feature essential for the support of subsequent discussion requires emphasis. I refer to the large changes in biological action attendent upon small changes in the N-alkyl group of analgesics e.g. if the N- CH_3 group in compounds I and II is changed to N-ethyl, N-propyl, N-allyl, a progressive loss in analgesic potency in the derived compounds results, and an anti-analgesic type effect is obtained from the latter compounds.

Furthermore, changes in the N- CH_3 group of the methadone and thiambutene-type compounds, and incorporation into ring systems gives interesting graded changes in the analgesic activities of the compounds.

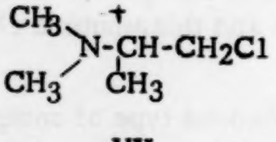
CONFIGURATION OF CERTAIN ANALGESICS

One possible explanation of observed differences in biological effects of enantiomorphs is associated with the three dimensional pattern of the molecules - the enantiomorph of a particular structure may present two but not three of the groups attached to the asymmetric centre in a similar manner to a suitable receptor (Slide 2).

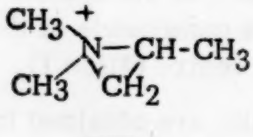
Because observed rotations give little information concerning the absolute configuration of compounds, it was important to establish the configurational relationships of the more analgesically active member of a number of analgesics possessing one asymmetric centre.

Slide 3 illustrates the synthetic methods used to establish the configuration of (-)- methadone, (-)-3-dimethylamino-1:1-diphenylbutyl ethyl sulphone, (+)-dimethylthiambutene and (+)-diethylthiambutene. These, the more analgesically active members of the various pairs, were then shown to have a configuration related to D-(-)-alanine (Wolff rearrangement presumed to proceed with retention of configuration - see later). (Slide 3)

The direct route using optically active VII



VII



VIII

for the condensation with diphenylacetonitrile could not be used in configurational proof because of the participation of the cycle immonium ion (VIII) in the reaction (see Slide 4). However, the lowering of the basic strength of the nitrogen centre in (VII) by the replacement of one of the N-CH_3 by the N-CHO group allowed the sequence illustrated in Slide 5 to be performed without the cyclisation interfering. The use of this sequence involving D-(-)-alanine gave (-)-methadone nitrile, the precursor of (-)-methadone. Because the optical purity of the intermediates in the series of reactions illustrated in Slide 3 had been demonstrated by the numerical

identity of their rotations with the isomers obtained by resolution of the corresponding racemic mixtures, the Wolff rearrangem ent involved in slide 3 had proceeded with complete retention of configuration. Thus the configurational relationship of the active analgesic isomers of Slide 1 with D-(-)- alanine is established unequivocally.

The identical configuration of (-)- phenodoxone (analgesically active isomer) and (-)-methadone was established using a comparison of the changes in the rotation of a series of compounds related to (-)-methadone with those of a series related to (+)-phenodoxone upon making changes in the polarity of the solvents in which the measurements were made. Opposite trend s are visible in the two latter series as indicated in Slide 6. The danger of using one member in each series only for configurational assignment is indicated by these figures.

The analgesically active methadone and thiambutene type isomers are thus configurationally related to D-(-)-alanine as shown in Slide 7

Stereoselective Adsorbsents.

It was also of interest to attempt to establish the configuration of (-)- morphine (I) with that of the (-)- morphinan series (II). Suitable methods for such investigations are not available. Investigation of the possiblity of preparing 'configurational footprints' in the surface of suitable adsorbents was, therefore, undertaken.

Slide 8 illustrates the results when the adsorbent silica gel was prepared in the presence of quinine and then the quinine molecules extracted from the surface of the dried powdered adsorbent. This stereoselective adsorbent adsorbed cinchonidine (same configuration as quinine) more strongly than the epimer cinchonine. In a similar manner quinidine-selective adsorbent adsorbs cinchonine m ore readily than cinchonidine. Configurational integrity of these footprints has been demonstrated for numerous cinchona alkaloids. (Slide 8).

The use of this method not only to obtain evidence of the configuration of morphinan-type compounds but also to provide models of an 'analgesic receptor' is being investigated.

CONSIDERATIONS CONCERNING 'ANALGESIC RECEPTOR SITES'

A difference in the biological effects of enantiomorphs could arise from differences in distribution and metabolism, or differences in the properties of the drug receptor combination as well as the difference in 'fit' of the enantiomorphs at a receptor. Consideration of metabolic studies of analgesic isomers, and the activities involving various analgesic antagonists, pointed to the probability of the latter being a suitable explanation in the analgesic field.

A tentative hypothesis concerning 'analgesic receptors' may, therefore, be formulated from a consideration of the three-dimensional structural features common to analgesic molecules.

Two features are common to all analgesics with an activity equal to, or greater than that of pethidine, namely, a tertiary basic group and a flat aromatic ring structure (or group capable of π orbital bonding). The same applies to analgesic antagon ists. We may assume that these represent two essential groupings which become

associated with specific receptor sites in a cellular boundary representing the primary site of action. However, a third reaction point must be considered if one is to account for the discrimination between isomers (see Slide 2).

Morphine (I) and morphinan type (II) compounds have rigid structures in which the relationship of the various asymmetric centres have been established. They were, therefore, examined for consideration of the most probable surface for presentation to a receptor of anionic type since morphine is about 80% ionised as a cation at physiological pH. Slide 9 illustrates these three dimensional considerations (in front of, behind, and in the plane of the paper are represented by ———, ... and ——— respectively)

It is postulated, therefore, that the receptor surface by which analgesic activity is mediated has the following three essential sites:-

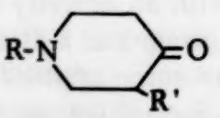
1. A flat position allowing of Van de Waals' forces bonding the aromatic ring of the analgesic drug or an area capable of interacting with a π-orbital system;
2. An anionic site.
3. A cavity suitably orientated with sites 1 and 2 is diagramatically represented in Slide 9.

The association of drug donor groupings with sites 1 and 2 then represents the primary site of analgesic action, whereas correct alignment of a projecting hydrocarbon residue with the cavity in one enantiomorph can enhance the drug receptor association but in the other enantiomorph the projecting group will impair the drug-receptor association.

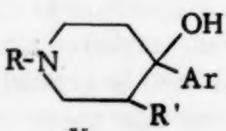
The synthetic analgesics of less rigid structures may be considered in terms of association with the above site. Considerations of models of methadone-and thiambutene-type compounds indicates conformations (see later for evidence) which would readily associate with the above analgesic receptor (see Slide 10); one isomer would allow better drug-receptor association than its corresponding enantiomorph. (Slide 10)

The reversed ester of pethidine, the prodines, may be represented or shown in slide 10; one isomer (<u>cis</u> Me/Ph configuration) would exist in a conformation allowing better association with the receptor than given by its diastereoisomer. However, the Roche workers had allocated the <u>trans</u> Me/Ph configuration to the more active isomer but their evidence was not unequivocal.

Preliminary results revealed that betaprodine (the analgesically more active isomer) hydrolysed more readily than alphaprodine, indicating the equatorial deposition of the ester group in the former compound and thus <u>cis</u> Me/Ph arrangement (see Slide 10). A series of compounds (X) was, therefore, prepared by the addition of aryl-lithium compounds to piperidones (IX).



IX



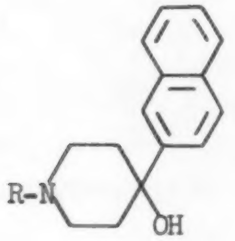
X

and the mixture of isomers in the products of the reaction carefully separated in many cases.

Investigation of the addition to the carbonyl group of tropinone has shown that the larger the attacking species, the more of the product formed by attack from the least hindered side of the carbonyl group was produced (Slide 11 - attack from side (b) favoured). A consideration of the conformation of N-alkyl-3-alkyl-4-piperidone would allow of assignments of configuration to the products of addition if the ratio of the stereoisomer products were determined (Slide 11) i.e. the trans Me/Ar compound should be formed in larger amounts. Addition of phenyl lithium gave isomers in the ratio of 3:1 and m- and p-tolyl lithium gave more of one isomer than the other. As expected, increasing the size of the species in the vicinity of the lithium gave a greater ratio e.g. an o-methyl or o-methoxy group (or the use of α -naphthyl lithium) led to the almost exclusive production of one isomer. All the isomers formed on major amount had a similar I.R. pattern which was completely different in a few wave-length regions from those exhibited by isomers formed in smaller amounts. Esters of certain of the compounds formed in major amount hydrolysed more readily than their corresponding isomers, indicating equatorial disposition of the ester group in the former compounds.

These results indicate the trans Me/Ar arrangement of the isomers formed in major amount. The isomers formed a minor amount will have a cis Me/Ar arrangement which will allow a more suitable conformation for association with the analgesic receptors: the higher analgesic potency of these isomers is thus explicable.

Consideration of the C-O stretching frequencies of compounds of type (XI)



XI

(in which the OH must be axially orientated) reveals the identity with the C-O stretching frequencies of the above isomers formed in major amount and thus provides further evidence for the above assignments.

Because of the flexibility and the possible rotation of these groups, the actual conformation of the above molecules upon adsorption at the site must be indeterminate. The design of suitable molecules by the incorporation of steric factors which exclude all but certain conformations is, therefore, of importance in a clearer understanding of the requirements of receptor sites. Slide 12 illustrates the approach in this field - only the marked conformations can exist. (Slide 12). It is of interest that only one isomer is formed (must be trans (Me/Ar)) and I.R. analysis indicates an axial OH group; the compound possesses analgesic activity.

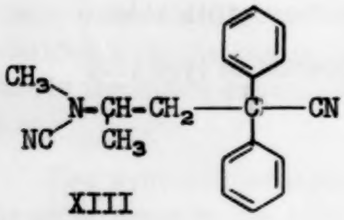
Conformation of the methadone-type compounds.

The planar phenyl groups of methadone-type compounds will tend to orient in positions of maximum clearance, that is to positions corresponding to the sides of a trihedral angle with the quaternary carbon at the apex (see Slide 10). The nitrogen atom will then be in a position to interact with the carbonyl group in a manner analogous to the transannular effect established for certain ring compounds (XII)

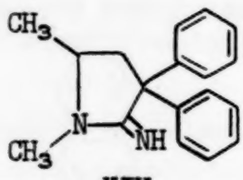
XII

Evidence that the nitrogen and carbonyl (or nitrile) groups are in close proximity is as follows.

(a) Chemical data indicates that at least the groups can approach each other readily, e.g. acid or alkaline hydrolysis, or even addition of Grignard compounds to (XIII) results in cyclisation to the iminopyrrolidine (XIV);

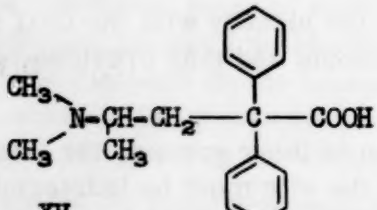


XIII

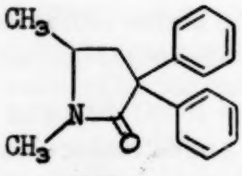


XIV

treatment of the acid (XV) with thionyl chloride results in cyclisation to (XVI)

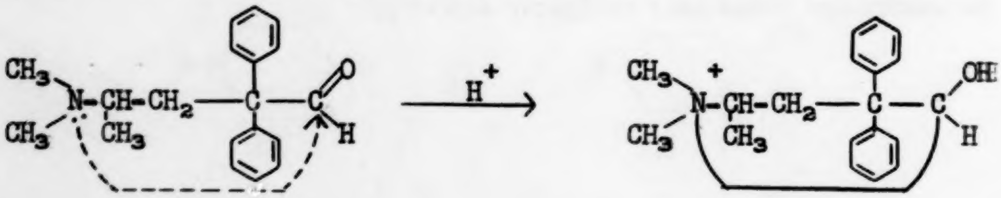


XV



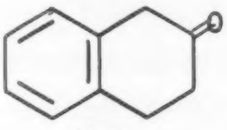
XVI

(b) Infra-red evidence indicates an interaction between the groups in question e.g. compound (XVII) exhibits a carbonyl absorption as the free base but not in the form of a salt (XVIII). Presumably the following occurs:

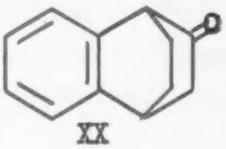


XVII XVIII

(c) It is known that, if a carbonyl group is suitably positioned in space in relation to an aromatic group, interaction of π -orbitals may occur with substantial enhancement of the carbonyl adsorption in the 280 to 300 $m\mu$ region e.g. (XIX exhibits normal carbonyl adsorption, whereas XX exhibits a much enhanced adsorption.



XIX



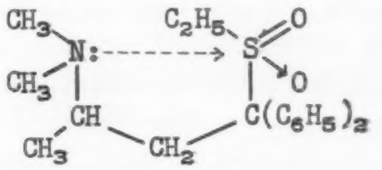
XX

since the carbonyl ring is now constrained into a semiboat conformation and π -orbital interaction occurs.

If the methadones adopt a conformation depicted in Slide 10, then carbonyl interaction with the phenyl rings should obtain. Substitution of methyl groups between the quaternary carbon and the basic group should enhance the interaction since the molecule will be then more rigidly held in the depicted conformation. Slides 13, 14 and 15 demonstrate that these effects occur.

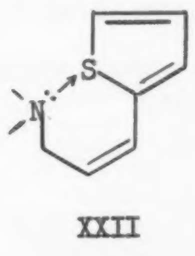
(d) The interaction between the basic centre and the carbonyl (or other similar group) should influence the observed dissociation constants. Branching of the chain between nitrogen atom and quaternary carbon should result in increased steric compactness and thus decrease the basic strength. The results for methadone type compounds (Slide 16) are in accord with these observations.

It is, therefore, concluded that methadones adopt the conformation depicted in Slide 10. It is reasonable to assume that the analgesic obtained by the replacement of the ketone group of methadone by the ethyl sulphone group is held in similar conformation by similar forces e.g. (XXI)



XXI

Dissociation constant measurements on the thiambutene-type compounds indicate Nitrogen-Sulphur interactions (XXII) and a conformation depicted in Slide 10.



XXII

INFLUENCE OF THE BASIC GROUP UPON ACTIVITY

Direct relationships between activity and dissociation constants of the compounds does not exist in analgesics (see slide 17).

However, the values for active analgesics lie within a fairly narrow range corresponding to dissociation, but not completely so, at physiological pH. Possibly some proportion of unionised molecules is necessary to give penetration of lipid membranes.

It has already been mentioned that small changes in the nature of the alkyl group can yield significant changes in the potency of many analgesics e.g. lengthening the dimethyl to diethyl and dipropyl in methadone gives a great reduction in activity; incorporation of such chain lengthening into a ring system does not result in reduction of potency.

It has also been postulated that association of the drug (as a cation) with an anionic site is important in the binding of drug to the analgesic receptors. It, therefore, seems reasonable to assume that steric limitations about the anionic site may be responsible for the above observed differences.

In methadone-type compounds, analgesic activities were therefore plotted against "width of basic group" - decreasing activities with increasing width were observed (slide 18). A similar trend was observed in thiambutene-type compounds.

The analgesic receptor site may, therefore, be represented as depicted in slide 19.

It is not implied that the association of a molecule with an analgesic receptor of necessity results in an analgesic response e.g. analgesic antagonists have all the stereochemical and physico-chemical properties to result in association with analgesic receptors.

The action of molecules at the analgesic receptor site may be regarded as depicted in slide 20 in which A represents an analgesic molecule and B an analgesic antagonist. Because these two types of molecules only differ by small changes in the alkyl group attached to the basic centre, it seems reasonable to assume they participate in the <u>same</u> biochemical change at the site. The results are then explicable if k_3 is much larger than k_6. Thus in the case of analgesic antagonists, X is formed so slowly that there is insufficient concentration produced in the presence of B to give a significant analgesic response.

Implied in the argument is the consideration that X - the primary product of the reaction of an analgesic (and anti-analgesic) at the receptor site is an analgesic itself <u>if supplied at the site</u>. Because analgesics and anti-analgesics only differ in the nature of the alkyl group attached to the Nitrogen, it seems reasonable to postulate that the group is involved in the primary reaction - possibly oxidative dealkylation is involved to liberate the <u>nor</u>-compound. Although <u>nor</u>-morphine has little activity by subcutaneous injection, administration by intracisternal injection indicated that the compound was at least as active as morphine itself.

It is, therefore, postulated that for an organic compound to exhibit high analgesic activity, the following features are important:

1. A basic centre which is partially ionised as a cation at physiological pH, in order that it may be able to associate with an anionic site in the receptor surface. A proportion of unionised molecules is probably necessary to facilitate penetration of cell membranes.

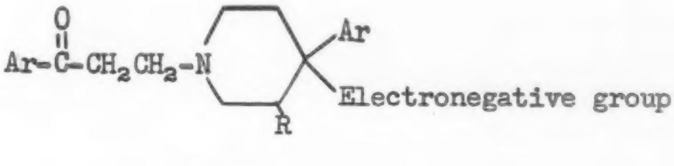
2. A flat aromatic structure (or unsaturated system) to allow strong collective Van der Waals' force bonding (or π-orbital interaction) with a flat portion of the receptor reinforcing the ionic bond mentioned on 1, which otherwise would not be sufficiently permanent because of ion exchange under biological conditions.

3. The basic group and the flat (or unsaturated) structure to be almost in the same plane; this to be accomplished by a completely rigid molecule or a slightly less rigid one held in the correct configuration by a steric or other constraints.

4. A suitably positioned hydrocarbon moiety (or unsaturated structure) to form a three dimensional geometric pattern; correct orientation of this moiety will facilitate but incorrect orientation will hinder drug receptor association.

5. A facile oxidative dealkylation of the alkyl group attached to the basic centre to yield a nor-compound.

Certain compounds have been designed in which cognisance of the above points has been taken, e.g. Mannich bases of the type (XXIII)



XXIII

have been shown to the potent analgesics. The great activity of a number of series of compounds has indicated the usefulness of the above hypothesis.

Much of the above information on which the above talk is based may be found in the following of our publications:-

Beckett, J. Pharm. Pharmacol., 1952, 4, 425.

Beckett and Casey, Nature, 1954, 173, 1231.

Beckett and Casy, J Pharm. Pharmacol., 1954, 6, 986.

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Beckett, Casy, Harper & Phillips, ibid., 1956, 8, 860.

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Beckett, Casy, Kirk, and Walker, J. Pharm. Pharmacol., 1957, 9, 939.

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Harper, Manufacturing Chemist, 1957, 28, 213, 271, 323.

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3 Canadian " 3

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July 13 - 18, 1958

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Venturella, Vincent	University of Pittsburgh
Verderame, Matthew	Albany College of Pharmacy
Voigt, Ralph	University of Illinios
Waldon, Curtis H.	University of Colorado
Weaver, Warren	Medical College of Virginia
Webster, George	University of Illinois

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Name	Institution
Webster, Victor	South Dakota State College
White, Allen	State College of Washington
Willette, Robert	University of Minnesota
Wilson, Charles	University of Texas
Wintter, John	Howard College
Worrell, Lee	University of Michigan
Yoder, David	Ohio Northern University
Zapotocky, Joseph	University of Arizona
Zimmer, Arthur	St. Louis College of Pharmacy
Zopf, Louis	State University of Iowa

PROGRAM

TEACHERS' SEMINAR ON PHARMACEUTICAL CHEMISTRY

Sunday, July 13, 1958

1:00-6:00	Registration Lobby, Centennial Hall
6:30 p.m.	Dinner Dining Room, Centennial Hall
8:00 p.m.	Opening Session George P. Hager, Presiding Dining Room, Centennial Hall
	Greetings from the University of Minnesota - William T. Middlebrook, Vice President, Business Administration
	Greetings from the American Foundation for Pharmaceutical Education W. Paul Briggs, Secretary and Executive Director
	Objectives of Teachers' Seminars - Louis C. Zopf, President, The American Association of Colleges of Pharmacy
	Pharmaceutical Chemistry Instruction in Great Britain - Arnold H. Beckett

Monday, July 14, 1958

Mayo Memorial Auditorium

Ole Gisvold, Chairman

8:00-9:00	Registration Auditorium Lobby
9:00	Opening Remarks
9:15	Pharmaceutical Chemistry Instruction for Professional Pharmaceutical Services - Harry W. Hind
10:00	The Undergraduate Pharmaceutical Chemistry Curriculum and Its Prerequisites - George L. Webster.
10:45	Coffee Break

11:00	Syllabi of Inorganic Pharmaceutical Chemistry Courses
	(1) Inorganic Chemist's Approach - Clarence A. Discher
11:45	(2) Pharmaceutical Chemist's Approach - Taito O. Soine
12:30	Lunch
2:00	Evaluation of Student Performance - Cyril J. Hoyt
3:00	Demonstration and Workshop

Tuesday, July 15, 1958

Allen I. White, Chairman

9:00	Opening Remarks
9:15	Syllabi of Organic Medicinal Products Courses (1) Basic Chemistry Aspects - Edward E. Smissman
10:00	(2) Pharmacologic Aspects - W. Lewis Nobles
10:45	Coffee Break
11:00	(3) Physiological Chemical Aspects - Kwan-Hua Lee
11:45	(4) Phytochemical Aspects - Ole Gisvold
12:30	Lunch
2:00	Interaction of the Students and Teacher in the Learning Process - Milton O. Pella
3:45	Picnic

Wednesday, July 16, 1958

Frank E. Di Gangi, Chairman

9:00	Opening Remarks
9:15	Syllabi of Courses in Drug Analysis - Lee F. Worrell
10:00	Syllabi of Courses Dealing with the Physico-Chemical Aspects of Medicinal Agents and of Dosage Forms - Alfred N. Martin
10:45	Coffee Break
11:00	Syllabus of a Course in Biological Chemistry for Pharmacy Students - Ernst R. Kirch

11:45	A Course in Forensic Chemistry - Arthur J. McBay
12:30	Lunch
2:00	Challenging the Superior Student in Undergraduate Instruction - J. William Buchta
3:00	Demonstration and Workshop

Thursday, July 17, 1958

George L. Webster, Chairman

9:00	Opening Remarks
9:15	Objectives of Higher Education and the Teacher's Role - Horace T. Morse
10:15	Special Training of Prospective Teachers during Graduate Residence - Gordon M. A. Mork
11:15	Coffee Break
11:30	The Teacher as a Research Director - Maurice L. Moore
12:30	Lunch
2:00	Criteria for Teacher Evaluation - Melvin W. Green
3:00	Demonstration and Workshop

Friday, July 18, 1958

Paul J. Jannke, Chairman

9:00	Opening Remarks
9:15	The Pharmaceutical Chemist's Heritage and Challenge in Research and Other Scholarly Pursuits - Walter H. Hartung
10:00	The Pharmaceutical Chemist's Need and Opportunity for Post-Doctoral Professional Development - Joseph H. Burckhalter
10:45	Coffee Break
11:00	Contributions to Recorded Knowledge by Pharmaceutical Chemists - Justin L. Powers
11:45	The Benefits of Consulting Activities to a Pharmaceutical Chemistry Teacher - Robert H. Miller

12:30	**Lunch**
2:00	**Factors Limiting the Duration of Drug Action - Bernard B. Brodie**
3:00	**Stereochemistry and Mechanism of Action of Synthetic Analgesics - Arnold H. Beckett**